VOLUME 5 FEBRUARY 1956 NUMBER 1

AUSTRALASIAN ANNALS OF MEDICINE

Journal of The Royal Australasian College of Physicians

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The journal is published quarterly in February, May, August, and November. The subscription rate is three pounds per annum, payable in advance to The Royal Australasian College of Physicians, 145 Macquarie Street, Sydney. Advertising rates may be obtained on application to Australasian Medical Publishing Company Limited, Seamer and Arundel Streets, Glebe, Sydney.

AUSTRALASIAN ANNALS OF MEDICINE

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DISSECTING ANEURYSM OF THE AORTA : A CLINICO–PATHOLOGICAL ANALYSIS OF 106 CASES[1]

J. V. HURLEY[2] AND J. H. W. BIRRELL[3]

From the Department of Pathology, University of Melbourne

"Virtually all present concepts regarding dissecting aneurysm have been based on analysis of small groups of cases or even of single cases." This is the introduction to the paper of Gore and Seiwert (1952), in which an analysis is made of the pathological features of 85 cases, the largest series yet recorded. Although some clinical data were available to these authors, they discuss only the pathological aspects of the disease, and their opening statement is still true of the clinical features of the condition. The paper of David *et alii* (1947) recording 17 cases from Boston is the best clinical study available. Full clinical and pathological records of 106 cases occurring in Melbourne since 1938 form the basis of the present paper, in which an attempt is made to determine both the incidence and the natural history of the disease as it occurs in this community, and also how its clinical diagnosis may possibly be improved. The only two previous Australian reports of a significant number of cases are those of Halliday and Robertson (1946), who report 19 cases from Sydney, and of Milazzo (1952), who reported 14 cases from Adelaide.

SOURCE OF MATERIAL

The present series of cases was obtained by a search of the records of the Melbourne teaching hospitals for the period 1938 to 1955. In addition two cases of dissecting aneurysm in young people found at autopsy by the coroner's pathologist have been included. Full clinical and autopsy notes and in many cases specimens and histological material were available for study. As the records of some of the hospitals are not so classified as to ensure that all cases occurring in the period studied have been located, no accurate estimate of the overall incidence of the disease in Melbourne is available. However, of the 106 cases, 51 came from the Royal Melbourne Hospital, where during the period of study 10,474 autopsies were performed, an incidence of 1 : 205. This corresponds closely with the figure of 1 : 228 cases found in Massachussetts General Hospital in the period 1937 to 1946. This series was partly concurrent in time with the present one, and like it derived from a large general hospital (David *et alii*, 1947).

Other figures in the literature varying from 1 : 714 to 1 : 143 are not so readily comparable, as the method of collection of cases varies widely. The figure of 1 : 500 quoted by Milazzo (1952) from Adelaide, although based on total deaths and not on total autopsies, is significantly lower. As the autopsy rate at the Royal Melbourne Hospital is in excess of 90% of all hospital deaths, this may account in part for the discrepancy ; the autopsy rate in Adelaide is not stated. Halliday and Robertson (1946) provide no figures on which the incidence in their cases can be calculated.

In comparison with hospital figures, the incidence in cases occurring at the City Morgue in Melbourne in the last few years has been 1 : 105 cases.

[1] Received on January 3, 1956.

[2] Stewart Lecturer in Pathology.

[3] Assistant Curator of Museum.

SEX AND AGE INCIDENCE

The age and sex incidence is shown in Table I, with the figures of David *et alii* (1947) for comparison.

The age distribution in the two sexes is shown in Figure I. The sex distribution follows closely that found in all series of dissecting aneurysms. Shennen (1934) in 300 collected cases found 65% male subjects and 35% female subjects, and most subsequent series have approximated to this figure. There are two noteworthy points:

FIGURE I

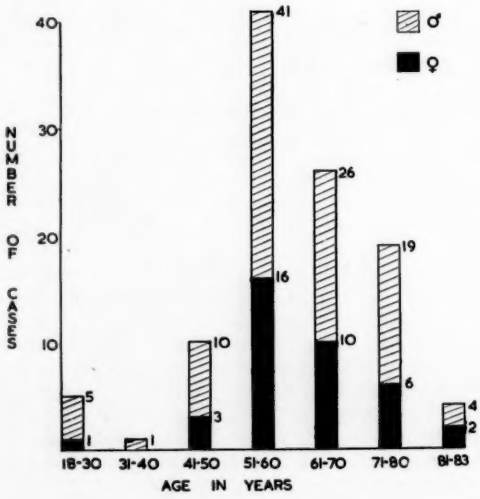

FIGURE I

Showing distribution of 106 cases of dissecting aneurysm according to age and sex

1. The age distribution and average age are almost identical in the two sexes, in contrast to the difference of eleven years in average age in the series from America. This age difference with sex has not been noted elsewhere in the literature where adequate figures are available, and is probably an artefact produced by the study of a relatively small number of cases.

2. Only two cases occurred under the age of forty years in the absence of Marfan's syndrome, and only six if these cases are included.

This agrees with David *et alii*, with Milazzo, and broadly with Halliday and Robertson, but is in clear contrast to the figures of Gore and Seiwert (1952), who report 38% of 85 cases in subjects aged under forty years, in a series largely from the Armed Forces Institute, and Shnitker and Bayer (1944) who report 24% of patients aged under forty years, in cases collected from the literature.

This gross discrepancy in age incidence is probably largely due to selective reporting of the exceptional cases occurring in young people. This point is admitted as probable by Gore (1953), and it is significant that in Shnitker and Bayer's (1944) figures most of their cases are reports of one or two isolated examples, many from the last century. The low total of 580 cases recorded up to 1944 shows conclusively that the common forms of this disease are not usually reported.

TABLE I

Age and Sex Distribution of 106 Cases of Dissecting Aneurysm

Series	Number of Patients	Age Extremes in Years[1]	Average Age in Years
Present series:			
Male	67	(18M) 33 to 83	61·4
Female ..	39	(24M) 42 to 83	61·7
David *et alii*:			
Male	12	47 to 69	55·0
Female ..	5	57 to 78	66·0

[1] The cases marked "M" were examples of Marfan's syndrome and the age of the youngest patient not affected by this syndrome is the second figure under "Age Extremes". David *et alii* had no cases of this type, and they have been excluded in the calculation of average age.

In an attempt to obtain further information about cases occurring in Australia in young people, the autopsy records of the Australian Military Forces for the period 1943 to 1946 covering approximately 2000 cases, have been examined. No case of dissecting aneurysm was found. It therefore seems certain that the disease occurs rarely in young people in this community and, unless some racial difference between Australia and America or Europe is operative, which appears unlikely, that the figures obtained by collection of reported cases gives a grossly misleading picture of the age incidence.

ÆTIOLOGY

Two factors of importance in their causation are obvious in the history of these cases, Marfan's syndrome and hypertension.

Marfan's Syndrome

Four examples of Marfan's syndrome were seen—three in males, aged eighteen, nineteen and twenty-one years, and one in a female, aged twenty-four years. This syndrome, commonly called arachnodactyly, was first described in 1896, and the wide variety of vascular abnormalities that may form part of

it has recently been reviewed by McKusick (1955). In brief, the syndrome consists of three elements as follows: (i). Skeletal lesions: a tall, thin build with long-tapered fingers *pectus excavatum*, and high arched "gothic" palate are the main features. (ii). Vascular lesions: of the many that may occur, hypoplasia with or without dilatation of the aorta and dissecting aneurysm are the two most common. (iii). Eye changes: congenital dislocation of the lens. It has been suggested that generalized abnormality of the elastic tissue is the common basis of these lesions (McKusick, 1955).

It seems that this congential lesion is the only common cause of dissecting aneurysm in this community, and the two cases occurring in its absence at the ages of twenty-nine and thirty-three years are to be regarded as the extreme lower end of the distribution curve of the age incidence of the more common form of the disease.

Hypertension

The data regarding the presence of raised blood pressure in these cases are shown in Table II. The criteria adopted with regard to blood pressure were as follows:

TABLE II

Blood Pressure in 102 Cases of Dissecting Aneurysm Marfan's Syndrome Excluded

Assessment	Number of Cases	
Clinically raised	37	62
Clinically and pathologically raised	25	
Pathological evidence only	26	
Normal clinically and pathologically	9	
No evidence	5	

The clinical criterion was a previous diagnosis of hypertension by a reliable observer or a record of a diastolic pressure of 100 millimetres of mercury or more. Purely systolic hypertension has not been included.

The pathological criteria were a heart weight in excess of 450 grammes at autopsy, with the increase in size affecting predominantly the left ventricle, in the absence of valvular or other mechanical cause for the hypertrophy.

It is certain that the majority of such enlarged hearts represent the presence of hypertension in life, but it is realized that in some cases coronary disease may cause cardiac enlargement in the absence of hypertension (Davis and Blumgart 1937; Harrison and Wood, 1949). Thus there is conclusive evidence of raised blood pressure in 62 cases, and presumptive evidence in a further 26, and it is absent with certainty in only nine cases.

That some cases of dissecting aneurysm may occur at all ages in the presence of a normal arterial pressure, was stressed by Shennen (1934), who records 25% of such cases in his review. The nine cases above support this view. But almost all series published since Shennen's stress the presence of raised pressure in the great majority of cases, especially if cases associated with vascular maldevelopment are excluded. David *et alii* (1947) report its presence in all 17 of their carefully studied cases. The inference is inescapable that raised arterial pressure is a major factor in the ætiology of the great majority of cases of dissection occurring in normally developed aortæ. Still further support for this conclusion may be drawn from the 11 chronic cases in this series, in which shock and other complicating factors in the acute phase are not operative. The blood pressure was raised in nine cases, the systolic pressure being in excess of 200 millimetres of mercury in seven of these.

In contrast to these two factors, no support can be derived from this series for the following two other factors stressed by some authors:

Exertion or Emotional Stress

The importance of physical or emotional stress has been emphasized by many, indeed most, authors on the subject. In some cases the statement has clearly been copied from paper to paper, and relatively few cases whose onset is clearly related to effort appear in the literature. Indeed, Milazzo (1952) repeats the usual statement regarding effort, when from the eight histories in his paper in which evidence regarding conditions at the onset of the attack is stated, it is clear that in seven cases the patient was at rest or sitting eating at the onset, and in only one case could effort be reasonably implicated as a possible cause.

Evidence regarding the condition of the patient at the onset of symptoms is available in 38 cases. This is summarized in Table III

There is no evidence to support sudden exertion, mental or physical, as a common precipitating cause of dissection, and also no suggestion that the proportion of cases in which details of onset are available is not representative of the whole series. A clear relation to severe exertion is unlikely to be overlooked in a clinical history; but its absence may well not be specifically noted.

Pregnancy

Pregnancy has been stressed by Shnitker and Bayer (1944) as an ætiological factor in cases occurring in females under the age of forty years; these authors report 24 of 49 such cases associated with pregnancy. Only one case of a young woman is present in this series, an example of Marfan's syndrome. Inquiry at the City Morgue and at the Royal Women's Hospital, Melbourne, reveals no record or recollection of a dissecting aneurysm related to pregnancy having occurred, and it must be concluded that such an association, if it occurs at all, is very rare in this community.

TABLE III

Conditions at Onset of Symptoms—95 Acute Cases

Evidence		Number of Cases
No evidence in history		57
Evidence available:		
(i) At rest	25	38
(ii) Mild exertion—mainly walking or eating a meal	9	
(iii) ? Severe exertion:		
Watching a football match	1	
At a meeting	1	
Working in yard	1	
Working in garden	1	

SYMPTOMS AND SIGNS

The clinical picture in dissecting aneurysm may assume many diverse guises. The cases in this series may be divided into several types as in Table IV.

TABLE IV

General Clinical Type—106 Cases of Dissecting Aneurysm

Type	Number of Cases
Patient moribund or in coma on admission	14
Severe chest pain	63
Severe abdominal pain	7
Peripheral vascular manifestation	2
Miscellaneous	9
Presented as a chronic lesion	11
Total	106

It is convenient to consider each of these groups of acute cases in turn; the chronic lesions are described separately below.

Patients Admitted to Hospital Moribund or in Coma (14)

The usual history in this group was that of a patient who suddenly lapsed into unconciousness, with or without premonitory symptoms of weakness or numbness involving one or more limbs, or of a patient found unconscious. In four cases frank hemiplegia was found on examination. The usual diagnosis made was of cerebral vascular accident, and in no case did the patient recover consciousness sufficiently to give an adequate history.

In no case in this group was the correct diagnosis made or suspected, and indeed there was no reasonable ground on which it could have been made.

In two cases in this group massive cerebral hæmorrhagic lesions originating in the vicinity of the internal capsule were found at autopsy. In one case the dissection involved the lower part of the right common carotid artery, and this may explain the cerebral lesion as an hæmorrhagic softening. In the second case, and in two others in which hemiplegia was found in the absence of macroscopic cerebral damage, the explanation is not apparent.

Patients Admitted to Hospital with severe Chest Pain (63)

This group of patients, comprising the majority, presented with the classical features of acute dissecting aneurysm. It is convenient first to describe the general picture and then to consider some aspects of it in more detail.

The patient usually complained of very sudden onset of pain of great severity, and often described it as of a tearing or bursting nature. The pain was commonly substernal in position at first, but early radiation to the back was common. In a number of cases the pain began in the back in the interscapular region, and spread forwards into the chest or down the lumbar part of the spine. The gradual migration of pain from chest to abdomen following the supposed progress of the aortic dissection, described as a common feature by some authors, was not seen in this series. Pain commonly persisted for many hours or even for several days if the patient survived for that period, and in many cases only partial relief was reported after full dosage with morphine.

Radiation of pain to the neck and jaw was described not uncommonly, but to the left arm in only a few cases; the latter was an uncommon complaint.

In patients with a pain of this kind the usual diagnosis was coronary occlusion, and this is the condition from which it is important that dissecting aneurysm be distinguished. This has recently become a more urgent problem with the widespread use of anti-coagulants in the treatment of patients with coronary

occlusion, as these must tend to reduce still further the already small chances of survival of patients with dissecting aneurysm.

A number of points of distinction between the two conditions have been stressed by Paul Wood (1937) and by David *et alii* (1947), and analysis of the present series provides the following information regarding them :

1. The complete suddenness of origin of the pain and its great severity were common findings, and seem to provide a real contrast with the usual case of coronary occlusion.

2. The severe chest pain was associated with abnormality of one or more of the main peripheral arteries This combination is almost diagnostic of dissecting aneurysm, and provides the majority of cases in which a successful diagnosis is made. It occurred in 21 cases in this series. The evidence of peripheral vascular impairment may take the following forms : (a) Numbness or coldness in a limb or limbs ; (b) Severe pain extending to a limb. In the left arm and less commonly the right, this may occur in coronary occlusion, but if it is severe it should always lead to a careful examination of the peripheral pulses ; (c) Absence or decrease of peripheral pulse, more especially if this is unilateral ; (d) Unequal blood pressures in the two arms. Any combination of these may, of course, occur. In this series the peripheral vessels involved are listed in Table V.

TABLE V

Involvement of Peripheral Arteries in 63 Patients with Severe Chest Pain

Artery Involved	Number of Patients
Carotid	3 (all with hemiplegia)
Brachial	6
Radial	2
Common iliac	4
Femoral	4
Femoral and radial	1
Femoral and carotid	1
Total	21

Of these 21 cases a correct diagnosis was made in 13 and in retrospect should have been made in six further cases.

3. Normal blood pressure was maintained in the presence of severe chest pain. This has been stressed by David *et alii* (1947) and by Weisman and Adams (1944), and is also favoured by Paul Wood (1937). Halliday and Robertson (1946) noted several cases which did not favour its use as a diagnostic point. The blood pressure on admission to hospital of patients with severe chest pain is summarized in Table VI. It will be seen that while the blood pressure remains high in some cases, it is low or normal on admission to hospital in almost two out of three cases, and thus is not a reliable guide in the separation of dissecting aneurysm from coronary occlusion. As the blood pressure is high before the onset in the great majority of cases of dissecting aneurysm, the high blood pressures on admission to hospital recorded by David *et alii* (1947) are probably merely a reflection of this fact, in

TABLE VI

Blood Pressure on Admission to Hospital of Patients with Severe Chest Pain[1]

Peripheral Vascular Signs	Low	Normal	High	Total
Present	2	9	10	21
Absent	16	13	13	42
Total ..	18	22	23	63

[1] High blood pressure has been taken as diastolic pressure in excess of 100 millimetres of mercury, and low pressure as a systolic pressure less than 100 millimetres of mercury. Diastolic pressure has been unrecordable in some cases and, together with the presence of free aortic regurgitation in others, makes impossible the separation of low blood pressure by diastolic readings.

that the blood pressure has further to fall to reach a low level than in cases of coronary occlusion, in most of which the initial blood pressure will be normal. It can also be seen from Table VI that the blood pressure level is of least use where it is needed most-in cases in which peripheral vascular manifestations are absent.

4. The pain spread to the back, or originated in the back. This would appear to be of diagnostic value. In 15 of the 42 cases of severe chest pain without peripheral vascular manifestations such radiation was present.

5. A pleural effusion developed. In 10 cases the presence of a pleural effusion, left-sided in nine, was noted soon after the patient's admission to hospital. In eight of these it developed under observation in hospital. This is to be related to the frequency with which rupture into the left pleural sac is found at autopsy. Such a unilateral effusion, especially if it is shown by aspiration to be blood, is almost diagnostic of dissecting aneurysm as against coronary occlusion ; but in several cases in this series, although the effusion was found, the diagnosis was still not made successfully.

6. Signs of aortic valve disease were present. The incidence of signs of aortic valve disease is

shown in Table VII. The occurrence of aortic murmurs in 17 (18%) of 95 acute cases is well in excess of the proportion of cases to be found by chance association, and of the proportion in cases of coronary occlusion. David *et alii* report aortic murmurs in nine of 16 cases, and Halliday and Robertson (1946) quote an expected incidence of 20%—without authority for this figure, however. Thus the presence of aortic valve murmurs in a case of severe chest pain of sudden onset is strong evidence for dissecting aneurysm.

In this series, in the 42 cases of acute chest pain without abnormality of a peripheral artery, the correct diagnosis was made eight

TABLE VII

Clinical Aortic Valve Lesion in Dissecting Aneurysm

Murmur	Acute Cases—95	Chronic Cases—11	Total
Aortic diastolic murmur with or without systolic murmur	13 (In 1, developed under observation; in 2, known to be present before attack)	4	17
Aortic systolic murmur alone	4	4	8
Total ..	17	8	25

times. By use of the criteria of pain in the back, pleural effusion and aortic valve murmurs it might have been at least strongly suspected in 16 more, or 24 cases in all.

In this series of 95 acute cases, coronary occlusion with recent myocardial infarction (two cases), and rupture of the coronary artery (one case) coexisted with a dissecting aneurysm of the aorta. No explanation of this is offered, although in both cases of infarction dissection had extended proximally to the aortic ring, so the infarct may have been due to interference with the coronary arteries at their origin. The autopsy report is not specific on this point.

Patients Admitted to Hospital with Severe Abdominal Pain (7)

The admitting diagnosis is listed in Table VIII. In all these cases the initial symptom was severe pain, apparently similar in type to that commonly arising in the chest, but restricted to the abdomen. In four cases, three diagnosed as renal colic and one as pancreatitis, it is significant that the pain was situated posteriorly.

Laparatomy was performed four times, and the correct diagnosis was suspected by the finding of retroperitoneal hæmorrhage in two of these cases.

In the case diagnosed as mesenteric thrombosis, melæna was present owing to dissection occluding the superior mesenteric artery at its origin.

One of the cases diagnosed as renal colic is of particular interest:

P.S., a male patient, aged eighteen years, complained of severe pain in the left lumbar region accompanied by hæmaturia three weeks before his admission to hospital. Whilst in the X-ray department for excretion pyelography, he suddenly collapsed with evidence of massive internal hæmorrhage. The plain X-ray film of the chest revealed the presence of a left pleural effusion, and after blood transfusion immediate thoracotomy was performed under the diagnosis of ruptured aortic aneurysm. The adventitia of the whole length of the descending thoracic aorta was plum-coloured, with blood oozing from multiple points. An attempt was made to resect and graft the affected area, but further rupture proximal to the graft caused the patient's death before the insertion of the graft could be completed. At the post-mortem examination the dissection involved the whole length of the aorta, with evidence of an earlier dissection at the origin of the left renal artery. The aorta was hypoplastic, and the usual skeletal stigmata of Marfan's syndrome were present.

No clear pointer emerges from this group of cases as to how the diagnosis could have been improved, although examination of the peripheral pulses is not recorded in several histories. and may have been valuable.

TABLE VIII

Admitting Diagnosis of Patients with Severe Abdominal Pain

Diagnosis	Number of Patients
Renal colic	3
Mesenteric thrombosis	1
Perforated peptic ulcer ..	2
Acute pancreatitis	1
Total	7

Patients Admitted to Hospital with Peripheral Vascular Manifestations

Apart from the 21 patients already discussed who had peripheral vascular impairment associated with severe chest pain, two further patients presented with such vascular changes as an apparently isolated lesion.

One patient presented with brachial artery occlusion of sudden and obscure origin following a " dizzy turn ", well-defined aortic regurgitation was present, and he died suddenly the next day.

The second patient presented with grossly unequal peripheral pulses following recovery from a painless

collapse of four hours' duration. The left common carotid and right femoral pulses were grossly decreased, and a pronounced aortic diastolic murmur was present. A diagnosis of dissecting aneurysm was made, and confirmed at autopsy next day after the patient's sudden death.

Miscellaneous Group

Nine cases do not fit into any of the above mentioned groups. Their main features are listed in Table IX.

The importance of these cases lies not in their mode of presentation, but in the fact that no pain was present. Together with the two cases of peripheral vascular occlusion without pain, there are 11 cases out of 95 in which extensive aortic dissection was apparently painless.

TABLE IX

Clinical Features in Nine Miscellaneous Cases

Clinical Features	Mode of Death
Congestive cardiac failure with aortic regurgitation	Died suddenly
Anæmia for three months; painless left pleural effusion	Died suddenly
Hypertensive cardiac failure	Died slowly over 17 days in hospital
Hypertension—aortic regurgitation, cardiac asthma	Died suddenly in an attack of cardiac asthma
Hypertensive cardiac failure	Died with intense dyspnœa without pain
Twenty-four hours' coma with recovery; hypertension; aortic regurgitation	Died suddenly; diagnosis, ? ruptured aorta
Chronic rheumatic heart disease	Died slowly of congestive heart failure
Hypertension	Died in attack of cardiac asthma
Chronic diarrhœa for five weeks	Died slowly

David *et alii* (1947) present two similar cases, but it does not appear to be widely appreciated that extensive aortic dissection occurs not uncommonly without pain. Two of these cases were successfully diagnosed—an uncommon happening.

NEUROLOGICAL COMPLICATIONS

Neurological complications are mentioned by a number of authors and considered in detail by Weisman and Adams (1944), who describe three types of nervous lesion which may complicate dissecting aneurysm.

Ischæmic Necrosis of the Brain

Ischæmic necrosis of the brain, due to involvement of the innominate or left common carotid artery in the dissection, may cause hemiplegia in the presence of an inadequate collateral circulation via the circle of Willis.

Seven cases of this type have been discussed above, three of them occurring in association with severe chest pain, and four in patients admitted to hospital in coma.

Ischæmic Necrosis of the Spinal Cord

Ischæmic necrosis of the spinal cord, causing paraplegia by involvement of lumbar and intercostal arteries supplying the spinal cord, has not been seen in this series.

Ischæmic Necrosis of Peripheral Nerves

Ischæmic necrosis of peripheral nerves is manifested by a cold pulseless weak limb with loss of tendon reflexes produced by spread of dissection to involve a major limb artery. Cases of this type in this series have been included under peripheral vascular manifestations, it not being considered possible to separate the direct vascular and indirect nervous elements involved in the production of such a state in a limb. It is noteworthy that in none of the cases of Weisman and Adams were the peripheral nerves examined histologically.

SUCCESSFUL DIAGNOSES

The correct diagnosis was made or strongly suspected in life in 24 of 95 acute cases, or 25%. There is evidence that the proportion of successful diagnoses has risen in the last few years, as of 51 cases in the last five years the correct diagnoses was made in 16, or 31%.

The strong impression from studying the histories in this series is that any improvement is due to the increased awareness of the condition, and not to any additional special diagnostic procedure. Once suspicion of the condition is aroused, successful diagnosis is a common sequel.

As was stated above, the correct diagnosis could reasonably have been made in a further 22 cases, giving a total of 46 in 93 cases. This closely corresponds to eight in 17 cases (David *et alii*) and 21 in 38 cases (Weisman and Adams), both from Boston, and is probably an approximation to the level of diagnosis which should be expected in first-class hospital practice.

SURVIVAL

The period of survival after the onset in 95 acute cases is shown in Table X.

Of the four patients discharged from hospital two are known to have died one and two months respectively after their discharge.

David *et alii* quote an average survival time of forty-three hours after the onset of the terminal episode.

Comparable figures are difficult to deduce from the present series; but of 91 patients who died in the acute attack, 40 died in the first twenty-four hours and most of the remainder within seven days of their admission to hospital.

It is impossible to determine from what population of acute cases the 11 cases presenting as a chronic lesion are derived, but it seems unlikely that the mortality of the acute attack is less than 90%.

TABLE X

Period of Survival of Patients with Acute Dissecting Aneurysm—95 Cases

Period of Survival	Number of Cases
Less than 24 hours	40
Less than 7 days	29
7 to 14 days	10
More than 14 days, but died in hospital	12
Discharged from hospital	4

MODE OF DEATH

The mode of death of these patients is summarized in Table XI.

It is seen that death is sudden in roughly one case in three. This may be painless and almost instantaneous; in several cases a patient seen a few minutes before, apparently comfortable, was found dead in bed.

TABLE XI

The Outcome and Mode of Death in 95 Cases of Acute Dissecting Aneurysm

—	Number of Cases
No recovery after onset	36
Gradual	22
Sudden death with or without recurrence of pain	33
Discharged from hospital	4
Total	95

Thus dissecting aneurysm must be included in the list of causes of sudden death—a point of some medico-legal importance.

PATHOLOGICAL ASPECTS

Cause of Death

The immediate cause of death in 75% of cases in this series was the dissecting aneurysm and its subsequent external rupture. Table XII lists the immediate cause of death and shows the incidence of the main sites of hæmorrhage. Some mediastinal hæmorrhage, for example, often accompanied a hæmothorax.

Rupture into the pericardial sac with resulting cardiac tamponade was the most frequent cause of death, and this is the general experience.

TABLE XII

Immediate Cause of Death in 103 Cases of Dissecting Aneurysm[1]

Cause of Death	Acute	Chronic	Total
Hæmopericardium	41	3	44
Left hæmothorax	20	1	21
Right hæmothorax	6	—	6
Retroperitoneal and/or mediastinal hæmorrhage	6	1	7
Intramural hæmorrhage	2	—	2
Others (cerebral hæmorrhage, cardio-renal disease *et cetera*)	17	6	23
Total	92	11	103

[1] The three survivors have been excluded from this table.

However, 23 patients died from causes other than external rupture, cerebral hæmorrhage and cardio-renal disease being the most common. Most of these 23 patients had well-advanced aortic dissections, though external rupture did not occur before death. It is possible in the several cases in which death occurred from cerebral hæmorrhage that the consequent rise in intracranial pressure led to reflex rise in blood pressure resulting in dissection of an aortic wall, already the site of medio-necrosis (Foster, 1955). In two cases the intramural hæmatoma was apparently sufficient to cause death.

Intimal Tears

The sites of the intimal tears, where present, are listed in Table XIII. Several points emerge. First, in 10 no intimal tear was found.

TABLE XIII

Sites of Intimal Tears in 103 Cases of Dissecting Aneurysm

Site of Tear	Number of Cases
Ascending aorta	55
Region of left subclavian artery	22
Abdominal aorta	9
Several tears	7
No tears	10

In these the disease must have been due to rupture of *vasa vasorum* with the formation of an intramedial hæmatoma. Twenty-three similar cases have previously been described (Gore, 1952). It is not possible to determine in how many more cases the disease began in

this way and was complicated by secondary rupture into the aortic lumen, as such rupture destroys any evidence of its origin; but it is not improbable that this is the usual mode of origin of the condition. Secondly, the most common site of intimal tears is in the upper ascending aorta and the arch at or immediately beyond the left subclavian artery, both sites where the aorta is relatively mobile. Thirdly, in a number of the cases several intimal tears were present. It may be difficult to decide at autopsy whether these are artefacts. The aorta splits easily even with careful dissection, so that a number of these multiple tears could have been caused by post-mortem handling. The intimal tear, although commonly transverse, may be in any direction, and varies from a small slit to a tear round the complete circumference of the aorta. The edges of the tear are usually sharply delineated.

The actual site of external rupture is always difficult to identify and was seldom mentioned in the protocols. Re-rupture, back into the arterial lumen, was also seldom mentioned.

Atherosclerosis

Atherosclerosis was noted as moderately severe to gross in 78 cases, a figure in line with the usual high incidence of aortic atheroma in this community. In only two cases was it specifically noted that the intimal tear was located through an atheromatous plaque or ulcer. The atherosclerosis probably binds the intima down to some degree, so that intimal rupture occurs away from atheromatous plaques.

Syphilis

Frank syphilis was present in one patient only, and she died from secondary hæmorrhage from a carcinoma of the breast. There is strong evidence that atheroma and syphilis play no part in the pathogenesis of dissecting aneurysm.

Extent of Dissection

The extent of dissection round the aorta is even more variable than the length of the dissection. Some dissection of the vessels in the neck and of the renal and the mesenteric vessels, when the abdominal aorta was involved, was common. Symptoms and signs related to this extraaortic dissection were less common, but in a patient in a state of collapse and often comatose, they may well have been difficult to elicit. This has been discussed above.

Condition of the Heart

The condition of the heart is of particular interest in view of the common antecedent history of hypertension. Table XIV shows that 77 patients had hearts which were stated to be either enlarged or grossly enlarged, or which weighed more than 450 grammes. In 10% of patients in this series gall-stones were found incidentally at post-mortem.

TABLE XIV

Size of Heart in 103 Cases of Dissecting Aneurysm[1]

Heart Size	Number of Cases
Greater than 450 grammes ..	51
Stated as grossly enlarged ..	5
Stated as enlarged	21
Less than 450 grammes ..	23
Unknown	3

[1] The three survivors have been excluded from this table.

Histological Findings

The histological findings will be dealt with in greater detail at a later date. Sections of aorta were available from 35 cases. In every case medial change was apparent of the general type described by Erdheim (1930) and many subsequent authors, and often a line of cleavage was present, with or without hæmorrhage, between the inner two-thirds and the outer third of the media. Occasionally some dissection occurred between the adventitia and media, but this was not common.

Aortic Valvular Disturbance

In 11 of 13 of the 16 acute cases in which data are available, distortion of the aortic ring by the extension of dissection back to the origin of the aorta will explain the production of a murmur.

In five of the 11 chronic cases the intimal tear was present at the site of the left subclavian artery, and in every one of these the aorta was considerably dilated, distorting the aortic ring even though dissection was well away from the valves. In the other three cases dissection occurred in the region of the valves.

Other mechanisms of production of the murmur have been suggested; but it is considered that the presence of a deformed or widely patent ring is the obvious and sufficient explanation for the great majority of cases.

Chronic Dissecting Aneurysm

A feature of this series is the occurrence of 11 cases in which the patients lived for periods varying from a month to six years after their aortic dissection. Six subsequently died from causes other than dissecting aneurysm.

TABLE XV

Tabular Summary of Clinical and Pathological Details of 11 "Chronic" Dissecting Aneurysms

Age (Years)	Sex	Mode of Onset	Blood Pressure (Systolic/Diastolic, Millimetres of Mercury)	Ante-Mortem Diagnosis	Duration of Disease	Cause of Death	Aortic Sounds	Post-Mortem Findings	Other Findings on Investigation
72	F.	Pain across shoulders	220/120	Congestive cardiac failure, bronchopneumonia	Unknown	Bronchopneumonia	—	Localized loss of media and intima in upper two-thirds of descending aorta	—
53	F.	Sharp pain in back and abdomen for two days	235/130	Congestive cardiac failure, tertiary syphilis, carcinoma of breast	Three years	Secondary hæmorrhage from carcinoma of breast	Systolic at base	Intimal tear at left subclavian; dissection to iliacs	X-ray: wide aortic arch and marked scoliosis; E.C.G.[1]: depressed I waves in leads II and III; Wassermann reaction positive
54	M.	Sudden sternal pain radiating to back	200/140	Congestive cardiac failure, coronary sclerosis	Twenty weeks	Uræmia	—	Tear at left subclavian; dissection down to iliacs	X-ray: grossly enlarged heart and severe lung congestion; E.C.G.[1]: left ventricular strain
58	F.	Nagging pain in left side of chest radiating to back	150/60	Leaking thoracic aneurysm	? Six years	Left hæmothorax	Generalized systolic	Tear in middle descending aorta down to iliacs	X-ray: widened, lengthened and calcified aorta; Wassermann reaction negative
64	M.	Throbbing intermittent chest and abdominal pain	190/130	Hæmoptysis and aortic aneurysm (thought first to be pancreatitis)	? Four years	Rupture into left lung	Diastolic	Tear at left subclavian; dissection to iliac vessels	X-ray: gross aortic shadow
47	F.	Stabbing pain in chest	260/160	Malignant hypertension and encephalopathy	Eight months	Hæmopericardium	Machinery murmur to left of sternum	Tear at left subclavian; dissection from valves to iliac vessels	X-ray: generalized cardiac enlargement and pulmonary congestion
76	M.	Hæmatemesis	230/140	Cerebral hæmorrhage	Two months	Cerebral hæmorrhage	Systolic at base	Tear above valves; dissection down to iliac vessels	E.C.G.[1]: left ventricular strain
61	F.	Ache in back and sciatica in left leg	230/110	Cerebral hæmorrhage	Five years	Cerebral hæmorrhage	Systolic at apex	Tears at innominate and cœliac arteries, being also limits of dissection	X-ray: cardiac enlargement with wide aortic shadow and scoliosis; gastric ulcer
53	M.	Sudden dyspnœa and pain in back	150/60	Aortic regurgitation; aortic aneurysm	Six weeks	Pericarditis and pneumonia	Diastolic at lower part of sternum	Tear above valves; dissection from valves to renal arteries	Wassermann reaction negative
21	M.	Fleeting anginal pain	125/30	Aortic regurgitation	Three and a half years	Ruptured ascending aorta	Diastolic at lower part of sternum	Tear above valves, localized chronic dissection in ascending aorta; hypoplastic descending aorta	Marfan's syndrome. X-ray: scoliosis. Grossly dilated aorta. Wassermann reaction negative
18	M.	Sudden abdominal pain	130/60	Appendicitis	Four weeks	Ruptured ascending aorta	—	Tear above valves; dissection from valves to iliacs; hypoplastic descending aorta	Marfan's syndrome

[1] Electrocardiographic.

These seems no adequate guide to which cases are going to become chronic, although in this series an intimal rupture at the level of the left subclavian artery without dissection back towards the heart would appear to afford the best prognosis.

It is not stated in many of the protocols whether or not re-rupture back into the " old " aorta has occurred, so that we cannot comment on the importance of re-rupture in prognosis. However, in many cases such re-rupture has clearly failed to protect the patient from early death from external rupture. The foramina left in the old aorta often appear sufficient for the maintenance of circulation in the absence of re-rupture.

An interesting point is the early development of atheroma in the new aorta, which must appear in some cases almost coincidentally with endothelialization of the new vessel.

Histological examination of the walls of some of these chronic dissecting aneurysms reveals a hyaline appearance, while in others medio-necrosis is found at another point, death resulting from subsequent rupture.

The main features of the chronic aneurysms are summarized in Table XV.

Marfan's Syndrome

Most congenital cardiac defects have been described occasionally as occurring as part of Marfan's syndrome. In the present four cases dilation of the aortic ring and ascending aorta with the occurrence of dissecting aneurysm were the main features. One patient had in addition a small patent *foramen ovale*, and another great stretching and sacculation of the aortic valve cusps.

A most striking feature in the three specimens available for examination was the extreme hypoplasia of the aorta. Histological examination of all of them revealed medio-necrosis not apparently different from that occurring in the absence of Marfan's syndrome. A more detailed study of the histology of these cases will be published shortly.

SUMMARY

The clinical and pathological features of 106 cases of dissecting aneurysm occurring in Melbourne are analyzed.

With the exception of a small group of cases occurring as part of the widespread congenital abnormality of Marfan's syndrome, the disease affects the middle-aged and elderly, with a sex preponderance in males of roughly 2 : 1.

In the great majority of cases both clinical and pathological evidence suggests precedent arterial hypertension as a major ætiological factor. A minority of cases occurs in its absence.

Effort or emotion bears no relation to the onset of the disease.

Cases in association with pregnancy have not been found.

The several clinical modes of presentation of the disease are analysed, and its differentiation from coronary occlusion has been discussed in detail.

The correct diagnosis was made antemortem in 25% of cases. Suggestions are made as to how this figure can be improved.

The natural history, prognosis and mode of termination of the disease are described.

ACKNOWLEDGEMENTS

We have to thank the honorary Medical Staffs of the Melbourne teaching hospitals for access to their records, and the Hospital Record Librarians for much valuable assistance. We also thank the City Coroner for the figures regarding the incidence of this disease in his autopsies, and the Director-General of Medical Services, Australian Military Forces, for access to wartime Army records.

This study constitutes an introduction to an experimental and histological study of dissecting aneurysm, which is supported by a grant-in-aid from the Life Insurance Medical Research Fund of Australia and New Zealand.

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BLOOD GROUPS AND DISEASE : RHEUMATIC FEVER[1]

R. J. WALSH[2] AND OLGA KOOPTZOFF[3]

From the New South Wales Red Cross Blood Transfusion Service, Sydney

THE ætiology of rheumatic fever remains unknown, although it is a disease causing much chronic disability and is of major importance amongst the factors responsible for fatal cardiac disorders. It seems unlikely that it is an inherited disease; but there is some evidence that the susceptibility to rheumatic fever may be genetically determined (Wilson *et alii*, 1948; Stevenson and Cheeseman, 1953). This statement implies that environmental factors, which almost certainly include contact with the hæmolytic streptococcus, are necessary to produce the disease in a susceptible individual.

If susceptibility to the disease is inheritable, it is unlikely that a single gene is responsible. More serious consideration must be given to the possibility of multifactorial inheritance. The coexistence in an individual of a number of different but specific genes may so modify his tissues during development that exposure to a certain environment will result in rheumatic fever. Conversely, the absence of one or more of the particular genes will provide an immunity to the diease in the same environment. Obviously it is difficult to establish such a mode of inheritance. Studies to investigate the role of genetic factors in rheumatic disease are generally undertaken in families of affected individuals, and are always open to the objection that the environment of siblings and parents is usually comparable with that of the patient.

The work reported in this paper is an attempt to detect some association between susceptibility to rheumatic fever and the blood groups. A direct chromosomal linkage appeared unlikely with a multifactorial hypothesis, but the predominance of a certain blood group gene or genes was possible. The investigation was stimulated because of the finding of an excess of group A amongst patients with carcinoma of the stomach (Aird *et alii*, 1953). A single gene obviously does not determine the occurrence of carcinoma of the stomach.

MATERIALS

Blood samples were obtained from 260 unrelated patients who were suffering or who had suffered from rheumatic fever. All were the children of Australian-born parents, and all had been treated in the Royal Alexandra Hospital for Children, Sydney. They were examined by members of the Institute of Child Health, Sydney, and fulfilled the requirements for diagnosis of rheumatic fever as defined by Duckett-Jones (1944) and accepted by the American Heart Association. In every instance the blood was obtained from the finger, two or three drops being collected into a small tube containing two millilitres of physiological saline solution.

METHODS

All blood samples were tested for the A B O groups with anti-A and anti-B sera, and all positive reactors with the anti-A serum were also tested with anti-A_1 serum. Three sera, anti-M, anti-N and anti-S, were used in the tests for the M N S groups. The Rh groups were determined with the aid of anti-C, anti-c, anti-D, and anti-E sera. The techniques employed were those described by Mollison *et alii* (1952).

The A B O and Rh gene frequencies were calculated by the methods outlined by Race and Sanger (1954). The M N S gene frequencies were obtained by the methods of Allison *et alii* (1952), which were described in detail by Walsh *et alii* (1954).

The distribution of blood groups in the series of rheumatic fever patients was compared with the distribution in various groups of white Australians. The χ^2 test as used by Race and Sanger (1954) was used for these comparisons.

[1] Received on September 13, 1955.

[2] Director, New South Wales Red Cross Blood Transfusion Service, Sydney.

[3] Serologist, New South Wales Red Cross Blood Transfusion Service, Sydney.

RESULTS

Distribution of Blood Groups

The distribution of the blood groups is shown in Tables I, II and III. The gene frequencies are shown in each instance, and the expected absolute numbers of each phenotype have been calculated from the gene frequencies. It will be seen that there is very close agreement between the observed and expected numbers; χ^2 was calculated for the observed and expected in each table, but the differences were not significant. This indicates that the group of patients was homogeneous within itself. The small deficiency in the expected numbers shown in Table III is due to the omission of those giving the reactions of Cde/cdE (++−+) and of Cde/Cde (+−−−). Samples giving these reactions were not observed.

TABLE I

A B O Groups of Children Who have Suffered from Rheumatic Fever[1]

Group	Observed Absolute	Observed Frequency	Expected Absolute	Australian Population Absolute
O	110	0·4247	110·5	500
A_1	92	0·3552	92·4	333
A_2	22	0·0849	22·1	95
B	24	0·0927	24·1	138
A_1B	8	0·0309	7·6	57
A_2B	3	0·0116	2·2	
Total	259	1·0000	258·9	1123

Gene Frequencies:
O = 0·6532
A_1 = 0·2166
A_2 = 0·0624
B = 0·0678
1·0000

[1] The blood of one patient in the series was not subgrouped for A; this patient has not been included in the table.

TABLE II

The M N S Groups of Children Who Suffered from Rheumatic Fever

Group	Observed Absolute	Observed Frequency	Expected Absolute	Australian Population Absolute
MS	60	0·2308	60·7	30
MsMs	28	0·1077	25·2	9
MNS	75	0·2885	74·1	40
MsNs	48	0·1846	53·0	27
NS	19	0·0731	19·2	13
NsNs	30	0·1154	27·8	21
Total	260	1·0001	260·0	140

Gene Frequencies:
MS = 0·2634
Ms = 0·3116
NS = 0·0981
Ns = 0·3269
1·0000

Comparison with Random Population

The distribution of the A B O groups of the patients with rheumatic fever was compared with that found by Simmons, Semple and Graydon (1951) amongst 1123 white Australians who were selected at random. This latter distribution is shown in Table I. It will be noted that in this series the group AB subjects were not divided into A_1B and A_2B. The χ^2 test gave a value of 4·52 for four degrees of freedom, indicating that there was no significant difference between the two series.

TABLE III

The Rh Groups of Children Who Suffered from Rheumatic Fever

Reactions with Antisera C	c	D	E	Most Common Genotype	Observed Absolute	Observed Frequency	Expected Absolute	Australian Population Absolute
+	−	+	−	CDe/CDe	51	0·1962	51·0	54
+	+	+	−	CDe/cde	94	0·3615	94·8	105
−	+	+	+	cDE/cde	35	0·1346	30·2	33
+	+	+	+	CDe/cDE	29	0·1115	32·6	45
−	+	−	−	cde/cde	39	0·1500	39·0	52
+	+	−	−	Cde/cde	1	0·0038	1·0	3
−	+	−	+	cdE/cde	3	0·0115	3·0	3
−	+	+	−	cDe/cde	6	0·0231	6·0	5
+	−	+	+	CDE/CDe	2	0·0077	2·0	0
Total ..				—	260	0·9999	259·6	300

Gene Frequencies:
CDe = 0·4380
cde = 0·3873
cDE = 0·1177
cDe = 0·0288
Cde = 0·0049
cdE = 0·0146
CDE = 0·0087
1·0000

The distribution of the M N S groups was compared with that found by Walsh and Montgomery (1947) in a series of 140 blood donors. There was no significant difference between the two series as shown by the χ^2 test (χ^2=3·34 for five degrees of freedom).

The control series used for comparison of the Rh groups was that reported by Simmons and Graydon (1950), who tested 300 white Australians selected at random. However, a χ^2 value of 3·26 for five degrees of freedom indicates that the differences between the two series are not significant.

CONCLUSION

It is apparent from these tables that there is no association between the A B O, M N S and Rh blood group sytems and the occurrence of

rheumatic fever. This applies only to the group of patients investigated; but it is believed that they were representative in all respects of rheumatic fever patients in general.

Susceptibility to rheumatic fever cannot be detected in an individual until he eventually develops overt manifestations of the disease. If the susceptibility rather than the disease itself is genetically determined, it is reasonable to conclude from the foregoing results that there is no association between the blood groups and this susceptibility. These negative findings do not invalidate in any way the hypothesis that susceptibility to rheumatic fever is genetically determined.

SUMMARY

Blood samples obtained from 260 unrelated patients who had suffered from rheumatic fever was tested for the A_1 A_2 B O, M N S and Rh blood groups. The observed distribution was compared with that found by various authors in the white Australian population, but no differences were detected. This negative finding does not invalidate the hypothesis that susceptibility to rheumatic fever may be inherited.

ACKNOWLEDGEMENTS

This investigation was conducted in collaboration with the Institute of Child Health, Royal Alexandra Hospital for Children, Sydney. Blood samples were collected only after the children had been examined by Dr. Helen Walsh and Dr. Bryan Dowd and had been found to satisfy the requirements for diagnosis of rheumatic fever. The authors wish to acknowledge their indebtedness to their collaborators and to Professor Lorimer Dods, Director of the Institute of Child Health, for his interest.

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A NOTE ON THE DISTRIBUTION OF A B O BLOOD GROUPS IN BRONCHIECTASIS AND PORTAL CIRRHOSIS[1]

B. P. BILLINGTON[2]

From the Department of Medicine, University of Sydney

CONSTITUTIONAL factors have been implicated from time to time in the ætiology of portal cirrhosis (Spellberg, 1954). In recent years there have been found significant variations from controls in the A B O blood group distribution in some diseases with a known hereditary factor. Carcinoma of the stomach has been associated with group A (Aird *et alii*, 1953), and chronic peptic ulcer, especially duodenal, with group O (Aird *et alii*, 1954). Other diseases with a known inherited tendency—for example, hypertension—have been shown to have no significant difference in the A B O blood group distribution as compared with a control population (Maxwell and Maxwell, 1955).

Similar data from small series of clear-cut pathological entities with rigidly defined diagnostic criteria will be worth assessing. The work here reported indicates that no significant difference in A B O blood group distribution as compared with a control population has been found in a hospital population of patients suffering from bronchiectasis. A highly significant association with blood group A as against blood group O has been found in a hospital population of patients suffering from portal cirrhosis when compared with a control population of blood donors and a control hospital population of bronchiectasis patients.

MATERIAL

The records of public patients at the Royal Prince Alfred Hospital, Sydney, have been analysed during the years from 1944 to 1954 inclusive, for all cases of bronchiectasis and portal cirrhosis in which blood group data were available. These comprise 149 subjects with morbid anatomical evidence of bronchiectasis, most frequently lobectomy specimens, in which there was no historical, clinical or pathological evidence of a specific exciting factor such as foreign body, tumour or tuberculosis. One hundred and eleven patients with blood group data satisfied the following criteria for portal cirrhosis—namely, histological proof, either at autopsy or by adequate biopsy, when the type of cirrhosis consisted of significant disturbance of hepatic architecture by fibrous tissue of portal distribution, without historical, clinical or pathological evidence of biliary tract disease, obstructive jaundice, syphilis, recent acute hepatic necrosis, metabolic (including pigmentary) or parasitic disease. The majority of these patients died as a result of hæmorrhage from œsophageal varices. No subjects included were immigrants to this country.

As a control, the figures from the A B O blood group distribution of 30,000 New South Wales blood donors from the New South Wales Red Cross Blood Transfusion Service, Sydney (Walsh, 1947), were used.

RESULTS

Table I shows the A B O blood group distribution in the blood donor, bronchiectasis and portal cirrhosis populations.

TABLE I

Distribution of A B O Blood Groups in Blood Donors and in Patients with Bronchiectasis or Portal Cirrhosis

Population	Total Number	A	B	O	AB
Blood donors	3000	11,514 (38·38%)	2912 (9·70%)	14,672 (48·91%)	902 (3·01%)
Bronchiectasis	149	52 (34·90%)	18 (12·08%)	77 (51·68%)	2 (1·34%)
Cirrhosis	111	65 (58·56%)	7 (6·31%)	37 (33·33%)	2 (1·80%)

Table II shows the A B O blood group distribution in the bronchiectasis hospital population compared with the expected frequency calculated from the total of blood donor and bronchiectasis populations. No significant difference is demonstrated.

Table III shows the A B O blood group distribution of the hospital cirrhosis population compared with the expected frequency calculated from the total of blood donor and hospital

[1] Received on September 21, 1955.

[2] Working with a part-time research grant from The Royal Australasian College of Physicians.

portal cirrhosis populations. It is apparent that there is a highly significant difference. For the four blood groups, when Yates's correction is used with three degrees of freedom, $\chi^2=17\cdot627$; when A and O groups only are taken, with one degree of freedom, $\chi^2=17\cdot116$.

Table II

Distribution of A B O Blood Groups in Patients with Bronchiectasis Compared with Expected Distribution[1]

Distribution	A	B	O	AB
Expected ..	57·16	14·48	72·89	4·46
Observed	52	18	77	2

[1] For A B O and AB (with the use of Yates's correction) $\chi^2=1\cdot76$ ($n'=3$); for A and O, $\chi^2=0\cdot697$ ($n'=1$).

The probability that this difference, favouring the incidence of cirrhosis in subjects of group A at the expense of group O subjects, is due to chance is less than one per 1000.

Table III

Distribution of A B O Blood Groups in Patients with Portal Cirrhosis Compared with Expected Distribution[1]

Distribution	A	B	O	AB
Expected ..	42·68	10·76	54·22	3·35
Observed	65	7	37	2

[1] For A B O and AB (with the use of Yates's correction), $\chi^2=17\cdot627$ ($n'=3$); for A and O $\chi^2=17\cdot116$ ($n'=1$).

Table IV shows the A B O gene frequencies in the portal cirrhosis group compared with the expected frequency, similarly obtained, calculated by the method of Dobson and Ikin (1946), in which the χ^2 for unreasonableness of group proportions is not significant. There is a highly significant association of portal cirrhosis with subjects carrying gene A, 56% above the expected value ($\chi^2=12\cdot922$); the statistical chances that this association is due to chance are less than one per 1000.

Table IV

Distribution of Gene Frequencies in Portal Cirrhosis Compared with Blood Donor and Expected Frequencies

Frequencies	A[1]	Non-A[1]	B[2]	Non-B[2]	O[3]	Non-O[3]
Blood donors	0·2353	0·7647	0·0663	0·9337	0·6983	0·3017
Expected	0·2359	0·7643	0·0668	0·9334	0·6975	0·3027
Observed cirrhosis	0·3807	0·6186	0·0521	0·9572	0·5765	0·4328

[1] $\chi^2=12\cdot922$; $P<0\cdot001$.
[2] $\chi^2=0\cdot364$.
[3] $\chi^2=9\cdot754$; $P<0\cdot01$, $>0\cdot001$.

Sex

The bronchiectasis group contained 61 males and 88 females, and the portal cirrhosis group 64 males and 47 females. There is no significant sex difference in A B O blood group distribution in the blood donor population (Walsh, 1955), and no significant difference in distribution from this population has been demonstrated for either sex in the bronchiectasis or portal cirrhosis groups; nor was any significant sex difference in distribution demonstrated between the bronchiectasis and portal cirrhosis groups.

Discussion

In selecting controls, Aird *et alii* (1954) have pointed out that in this type of study comparisons with consecutive blood donor registrations from the same area are legitimate and likely to be unbiased, but that it is advisable to prove that the hospital population does not differ significantly from the blood donor population. In this latter respect a satisfactory method of control is to show that, in the hospital under consideration, certain diseases yield blood group frequencies which do not differ significantly from those of the blood donor controls. In this series, no difference in blood group frequency has been demonstrated in the hospital population of bronchiectasis subjects compared with the blood donor population. Further, in this series of hospital patients there is a highly significant difference in the distribution of A B O blood groups, between the bronchiectasis and portal cirrhosis patients; for all blood groups with three degrees of freedom $\chi^2=15\cdot085$, and for A and O groups alone, with one degree of freedom, $\chi^2=12\cdot795$.

Under these circumstances it appears that the demonstration of a highly significant association between blood group A and this hospital population of patients with portal cirrhosis is valid.

It will be allowed that the group of patients with portal cirrhosis admitted to the series is highly selected, by virtue of the necessity of blood group data being available, in most instances by the incidence of gastro-intestinal bleeding or the presence of anæmia. However, there is no reason to suspect that this selection could alter the results, although, before final acceptance of the association, further work must demonstrate that such selection is not important.

Fraser Roberts (1955), in discussing the results of other surveys, has recently sounded a warning on the acceptance of evidence without reasonable caution. He states the importance of rigid criteria for admission of cases to blood group series, and demands that the degree of significance found in an association between a disease and a change in blood group distribution should be at least one per 1000 when there is no ancillary evidence that such an association might exist, to allow a margin for error in the control population, and to cover other unsuspected factors. In this instance, with portal cirrhosis all these criteria have been met, and it would appear therefore that an association with blood group A can be established.

The statistical methods employed cannot demonstrate any reason for such an association, nor do they indicate any causality in the association. It is beyond the scope of this note to discuss possible reasons for an association, although Lea (1953) has recently shown in a group of English ex-servicemen that there is a highly significant association between cirrhosis and dark subjects as opposed to blond, based on criteria of eye and hair colour, when compared with a control population of ex-servicemen, and he ascribes this to an inherited factor of susceptibility to cirrhosis.

Further work, therefore, seems necessary to confirm an association between blood group A and portal cirrhosis, particularly in other areas, and to elucidate reasons for this suggested association.

Conclusions

No significant difference in A B O blood group distribution has been shown in patients suffering from bronchiectasis when compared with a control population of blood donors.

In portal cirrhosis patients, it has been demonstrated that there is a highly significant association with blood group A at the expense of group O, when compared with blood donors or patients suffering from bronchiectasis acting as a control hospital population. The increase in group A is 56% above the expected value.

No obvious reason is advanced for this association; further data are required from other places to confirm these findings.

Acknowledgements

I am indebted to the General Superintendent and the Medical Records Librarian of the Royal Prince Alfred Hospital, Sydney, and to Dr. H. O. Lancaster, School of Public Health, University of Sydney.

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FURTHER OBSERVATIONS ON THE TREATMENT OF LEPTOSPIROSIS[1]

R. L. DOHERTY[2]

From the Queensland Institute of Medical Research, Brisbane

THE clinical features and treatment of 115 patients with leptospirosis in North Queensland were discussed in a previous paper (Doherty, 1955). It was pointed out that the clinical picture was mild in comparison with previous Australian series. This could have been due, partly to the recognition of new serotypes of lower virulence, and partly to a more complete diagnosis of mild cases due to the serotypes known previously. However, the contrast in mortality, in the number of patients jaundiced, and in the duration of fever was so striking that it seemed probable that the antibiotics given to most patients had modified the course of their disease.

The number of patients who did not receive antibiotics in that series was small; it was pointed out that they represented a special group of mild cases, but even so their average total duration of fever was longer than that of any treated group. Larger groups received penicillin in one of three grades of dosage; it was shown that patients who received 4,000,000 units of penicillin per day had a shorter average total duration of fever, and a shorter average duration of fever after treatment, than patients who received 800,000 units per day. Statistical analysis of the same figures from smaller groups of patients infected with *Leptospira australis A* or *australis B* suggested that the conclusions remained valid when limited to a single serotype.

A further 158 patients with leptospirosis have been studied at the Innisfail Field Station. The total group of 273 patients now available for analysis permits a more precise assessment of several variables than was possible in the previous paper.

DIAGNOSIS

One hundred and fifty-six cases of leptospirosis were diagnosed by the isolation of leptospiræ and the demonstration of an antibody response in paired sera. Eight were diagnosed by isolation only, as the patients could not be traced for examination of convalescent sera. One hundred and five cases were diagnosed by agglutination tests on paired sera. Four are included in which the diagnosis rests on the clinical picture and high antibody titres in convalescent sera, no sera from the acute stage being available for testing.

The following serotypes were represented: *icterohæmorrhagiæ*, seven; *canicola*, 15; *australis A*, 88; "Esposito", one; *australis B*, 69; "Robinson", 14; *pomona*, six; *hyos*, 13; *medanensis*, three; "Kremastos", 31; "Szwajizak", 10; "Celledoni", 14; "Valbuzzi", one; double infection (*hyos*-"Szwajizak"), one.

CLINICAL FEATURES

The mortality was nil. Two hundred and sixty-six patients had clinical features showing no significant differences from those described in detail in the previous paper. These include severe prostration and high fever on admission to hospital, with headache, muscle pains, sore eyes, liver tenderness, and enlargement of lymph glands. It is not proposed to list the signs and symptoms in detail; but it should be recorded that one patient infected with "Celledoni" and one with *medanensis* were thought to be jaundiced for a short period. A rise in serum bilirubin level was not demonstrated in either; but the observations are of interest as the first records of jaundice in patients infected with those serotypes.

Seven patients did not make an uninterrupted recovery. Two developed uræmia, and one of them became grossly jaundiced; five, including one of the previous two, developed uveitis in convalescence; one had leptospiral meningitis, confirmed by lumbar puncture.

The histories of the two patients who became uræmic are as follows:

C.J., aged forty-five years, a railway carpenter, of Redlynch, near Cairns, was admitted to the Cairns Base Hospital on April 26, 1954. He later gave a history that he had fallen ill on about April 12 with feverishness, headache, shivering, severe vomiting and weakness of the legs. His family said that he had been delirious at times. He did not seek medical attention during this period. For the week prior to his admission to hospital he felt weak and had severe

[1] Received on September 26, 1955.

[2] Senior Research Fellow.

diarrhœa, but did not feel feverish. Three days before his admission to hospital he noticed that he was jaundiced.

On examination, he was jaundiced and dehydrated, and had cold extremities, a feeble pulse and a dry mouth. His blood pressure was 70 millimetres of mercury, systolic, and 40 millimetres, diastolic, and his liver was palpable one inch below his right costal margin. He had no neck stiffness; the admitting officer described a rash on his legs, but this was not recorded again. His spleen was not palpable.

The patient had worked at the Cairns railway yards, and gave no history of exposure to scrub or cane. His family said that he drank heavily. On his admission to hospital therefore he presented a clinical problem; the provisional diagnosis was "hepatitis with cholæmia". Hydration was restored and maintained by the intravenous administration of glucose-saline solution. On April 27 he passed small amounts of urine. On April 28 he was drowsy and apathetic, but could take fluids orally. His serum urea level on April 30 was 235 milligrammes per 100 millilitres. He recovered gradually; by May 20 he was able to walk about the ward, and he was discharged from hospital soon after. The results of liver and renal function tests performed during and after his illness by Dr. W. Horsfall of the Commonwealth Health Laboratory, Cairns, are listed in Table I.

The patient was readmitted to hospital on June 17 complaining of blurring of vision present for the previous week. On examination, he was found to have bilateral cyclitis; his fundi were obscured by a vitreous haze and keratic precipitates were present in the anterior chambers. The condition subsided with treatment, and he was finally discharged from hospital six weeks later.

Cyclitis following an illness with jaundice and uræmia made the diagnosis of leptospirosis very probable. Serum taken on the seventeenth and twenty-fifth days had high agglutinin titres (3000) against *australis A*.

H.B., aged thirty-seven years, a carpenter, of Innisfail, was admitted to the Innisfail District Hospital on April 1, 1955. He had a convulsive seizure on arrival at hospital and was comatose on his admission. Later it was learnt that he had fallen ill on March 23 with headache and nausea; he had worked that day, but felt feverish next day, with diarrhœa and vomiting, and remained in bed. He considered himself to have "the flu", and treated himself with rum. On March 29 he felt no better, and attended the out-patient department. He was thought to have gastro-enteritis, and was given a bismuth mixture and allowed to go home. During the week before his admission to hospital he had noticed that his urine was scanty. He had a history of minor head injury two years before, but otherwise had been in good health. For several weeks before he fell ill he had been dismantling an old house on the edge of scrub near Mourilyan Harbour, where many rats had been disturbed.

On examination, the patient was comatose; his temperature was 100° F., he had no neck or back stiffness, and small glands were palpable in his axillæ and groins. His liver and spleen were not palpable, his heart sounds were normal, and his blood pressure was 125 millimetres of mercury, systolic, and 65 millimetres, diastolic. He was given penicillin, 300,000 units every six hours; two further epileptiform convulsions that evening were controlled with paraldehyde given intramuscularly. Lumbar puncture at 6 a.m. on April 2 produced blood-stained fluid, but the blood was considered to be from trauma from the needle. His condition later that morning had deteriorated, his temperature was 103° F., and he was cyanosed and dehydrated and looked moribund. The small amounts of urine passed contained heavy deposits of albumin. He had definite left-sided weakness and spasticity, with patellar and ankle clonus. The intravenous administration of glucose-saline solution was commenced, and he was given "Terramycin" intravenously, 500 milligrammes in each litre of fluid. His blood urea content that evening was 260 milligrammes per 100 millilitres. He was still comatose on April 3, and had pronounced muscle twitching. However, his urinary output was 600 millilitres and this amount increased each day. By April 5 he was reacting to stimuli sufficiently to swear at the nurses tending him. His temperature was normal that day and his urine contained no albumin. His blood urea content was 300 milligrammes per 100 millilitres. It was possible to feed him by mouth, and the "Terramycin" therapy was continued orally.

Thereafter he improved slowly. On April 13 he could speak clearly; his blood urea content fell to

TABLE I

Results of Liver Function Tests on C.J.

Day of Illness	Serum Bilirubin Content (Milligrammes per 100 Millilitres)	Serum Alkaline Phosphatase Content (King-Armstrong Units *per Centum*)	Serum Proteins (Grammes *per Centum*)	Thymol Turbidity (Units)[1]	Thymol Flocculation	Zinc Sulphate Turbidity (Units)[1]	Response to Colloidal Gold Test	Paper Electrophoresis	Serum Urea Content (Milligrammes per 100 Millilitres)
16	11	7	5·2	—	—	3	—	"Albumin appeared lowered"	—
19	—	—	—	—	—	—	—	—	235
25	1·8	—	6·9	—	—	—	—	—	49
72	<0·5	8·5	7·2	11	Negative	12	+++	"Globulin definitely raised"	37·5
96	<0·5	7·5	6·1	10	Negative	10	Negative	—	34
127	<0·5	10	5·9	5	Negative	8	Negative	—	—

[1] Normal thymol turbidity, 0 to 4 units; normal zinc sulphate turbidity, 2 to 8 units. This test was carried out by Kunkel's technique (1947), but with the use of MacLagan's thymol turbidity standard.

44 milligrammes per 100 millilitres on May 12. His convalescence was retarded by hypostatic pneumonia and a bed sore; these may have been responsible for a twenty-two-day period of fever commencing on April 9, which showed no response to antibiotics. This may also have corresponded to the secondary fever seen (in a less florid form) in about one-third of cases of leptospirosis in North Queensland.

He showed no jaundice or biliuria; his temperature chart is shown in Figure I. Examination of serum

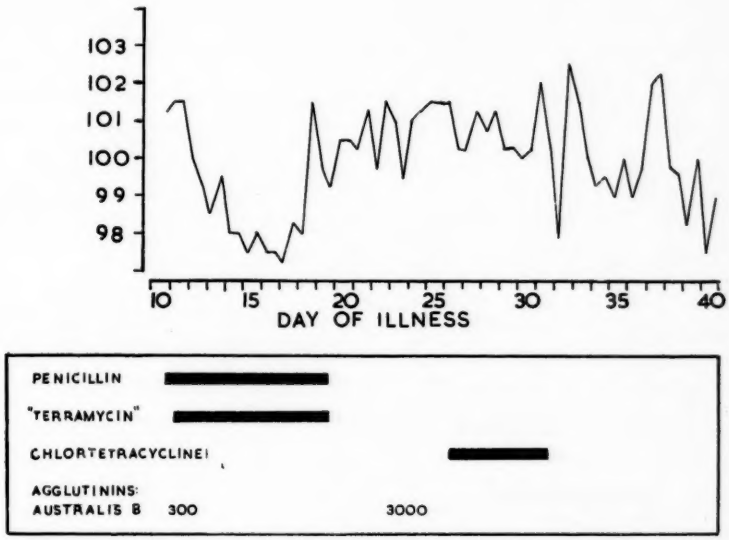

FIGURE I

Temperature chart of H.B.; *australis B* infection with uræmia

taken on the eleventh and twenty-third days of illness showed a rise in agglutinin titre from 300 to 3000 against *australis B*, and from 10 to 300 against "Robinson".

Five patients developed iritis, cyclitis or iridocyclitis. Their data are analysed in Table II.—The case history of one (C.J.) has been given above. The interval between the onset of the primary attack of leptospirosis and the appearance of eye complications ranged from nineteen days to four months. The condition was bilateral in two patients. Four received penicillin during the acute attack, two in high dosage. There is, therefore, no evidence from this series that treatment lowers the incidence of this complication. Johnson (1950) described iritis or iridocyclitis in four of 105 patients infected with *pomona*, most of whom did not receive penicillin.

One patient had abnormal findings on lumbar puncture. His history is as follows:

R.B., aged thirteen years, a schoolboy, of Gordonvale, was admitted to the Gordonvale Memorial Hospital on April 14, 1954. He gave a history of feverishness, headache, nausea and vomiting of two days' duration. He had no cough, but had a sore throat.

On examination of the patient, his temperature was 101·5° F., he had an enlarged tender gland in his right groin, and his abdomen was tender under the right costal margin, but his liver was not palpable. His

TABLE II

Details of Five Patients with Post-Leptospiral Uveitis

Patient	Age (Years)	Serotype	Treatment in Primary Illness	Interval between Onset and Development of Uveitis	Description of Eye Lesions
L.B.	27	*pomona*	Penicillin, intermediate dosage	4 months	Right iritis
L.I.	11	*australis B*	Penicillin, low dosage	1 month	Bilateral iritis
C.J.	45	*australis A*	Nil	2 months	Bilateral cyclitis
J.M.	39	*australis B*	Penicillin, high dosage	19 days	Left iritis
C.Z.	35	*australis B*	Penicillin, high dosage	22 days	Right irido-cyclitis

neck was stiff. No other abnormalities could be found. The provisional diagnosis was leptospirosis, and treatment was commenced with penicillin, 250,000 units being given every three hours. On April 16 he was still febrile; penicillin therapy was stopped and "Chloromycetin Palmitate" was given, 750 milligrammes *statim* and 375 milligrammes every six hours. He was afebrile on April 18; on April 19 his temperature reached 99·6° F., and he vomited and complained of headache. His neck and back were stiff. Lumbar puncture produced sterile, turbid fluid containing 616 cells per cubic millimetre (62% polymorphonuclear cells, 38% mononuclear cells) and 134 milligrammes of protein per 100 millilitres. He recovered quickly, and was discharged from hospital on April 23.

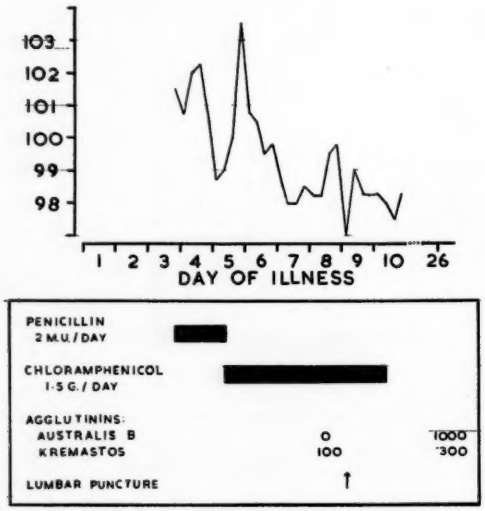

FIGURE II

Temperature chart of R.B.; *australis B* infection with meningitis

Examination of serum taken on the eighth and twenty-sixth days showed the development of agglutinins against *australis B* to a titre of 1000. There was evidence also of previous infection with one of the *hebdomadis* group. His temperature chart is shown in Figure II.

Gsell (1952), discussing meningeal involvement in leptospirosis, distinguished "meningism"—occurring with the first episode of fever, when the cerebo-spinal fluid contains no cells and is normal to chemical tests, but leptospiræ can be grown from it—from "meningitis", occurring with the secondary fever, when there may be a large number of cells in the fluid, but no leptospiræ can be grown from it. In the case described both were present clinically, but no lumbar puncture was performed during the primary fever.

A secondary rise in temperature, lasting one to four days, occurs between the fifth and fifteenth days of illness in one-third of North Queensland cases of leptospirosis. The majority of patients showed no new signs or symptoms at that time, but some complained of headache and nausea. Several others developed signs of meningitis similar to R.B. No lumbar puncture was performed as the diagnosis was not in doubt; but it is probable that they had similar changes in the cerebro-spinal fluid. All recovered quickly.

ANALYSIS OF TREATMENT

It can be stated from the foregoing case histories that two patients, who received no antibiotics during the acute febrile stages of their illness, had clinical courses far more severe than those of any treated patient. This in itself supports the contention that the antibiotics are of value; but one would hesitate to base conclusions on two patients. The most satisfactory criteria available by which rival therapeutic regimes can be assessed are the total duration of illness from onset, and the duration of fever after treatment was commenced.

It must be pointed out that all patients were admitted to hospital and treated by their own doctors. It was not considered justifiable to withhold treatment from any but the most mildly affected patients; the untreated group therefore consists mainly of patients who were thought to have some other febrile condition (for example, influenza), and whose condition was diagnosed only in retrospect. It was not possible to run controlled series, as there was no way of determining the serotype on the patient's admission to hospital. The practitioners were asked to choose one of three penicillin dosages—100,000 units three-hourly, 400,000 units four-hourly and 500,000 units three-hourly. Beyond that, no attempt was made to influence their treatment.

The duration of fever after treatment was measured from the giving of the first dose of an antibiotic to the first temperature reading taken on the first day (from midnight to midnight), during which the temperature of the patient did not rise above 99° F. This was intended to exclude the secondary rise in temperature; there is no evidence that the secondary rise is affected by the treatment given. In a few cases the temperature chart suggested a secondary rise, but the afebrile period was less than twenty-four hours. Rigid enforcement of the foregoing definition may therefore have given a false high value in

several cases, but it was considered necessary in order to standardize the groups.

It was mentioned in the previous paper that it was impossible to analyse any bias due to the hospital at which the patients were treated, as separate from that due to the antibiotics. The possibility that some unrecognized factor might be operative seemed unlikely, but could not be excluded with certainty. The larger size of the present series made it possible to compare patients, infected with the same serotype and treated with different regimes at the same hospital (for example, various patients infected with *australis B* were treated at Innisfail with penicillin in high dosage, penicillin in low dosage or no antibiotic). It was also possible to compare groups of patients infected with the same serotype, and given the same treatment, but treated at different hospitals. In neither case was there any suggestion of the presence of any unrecognized factor (Table III).

TABLE III

Durations of Fever in Australis B Infections Treated at Different Hospitals

Place of Treatment	Group A (No Antibiotic)		Group D (Penicillin, High Dosage)		
	Number	Average Total Duration of Fever (Days)	Number	Average Total Duration (Days)	Average Duration After Treatment (Hours)
Innisfail ..	5	6·8	8	4·4	36
Other hospitals ..	6	7·8	7	4·8	38
Standard errors of differences		0·8	—	0·8	6·6

Exact details of duration of fever and antibiotic dosage are available for 264 patients, who can be divided into the following six groups: A, no antibiotics; B, penicillin, 800,000 units daily; C, penicillin, intermediate dosage (1,000,000 to 3,000,000 units daily, but in most cases 2,400,000 units daily); D, penicillin, 4,000,000 units daily; E, a broad-spectrum antibiotic; F, more than one antibiotic. The number of infections with each serotype falling in each group is shown in Table IV.

Results of Penicillin Treatment

Australis A.—Eighty-five patients were infected with *australis A* or "Esposito" (which is very closely related to *australis A*). The average total duration of illness, average duration after treatment, and average day on which treatment was commenced for the various treatment groups, are shown in Table V. Only a small number of patients received penicillin in low dosage, but their results are significantly worse than those of patients given the higher dosages. Patients given intermediate and high penicillin dosages had results that did not differ significantly from each other. This suggests that, for *australis A* at least, a dosage of 400,000 units of penicillin four-hourly is as effective as a dosage of 500,000 units three-hourly.

One of the three untreated patients had a very mild illness lasting only three days. This

TABLE IV

Cases of Each Serotype Allotted to Treatment Groups

Group	Treatment	*icterohaemorrhagiae*	*canicola*	*australis A*	"Esposito"	*australis B*	"Robinson"	*pomona*	*hyos*	*medanensis*	"Kremastos"	"Szwajizak"	"Celledoni"	"Valbuzzi"	Mixed	Total
A	No antibiotic ..	—	—	3	—	11	1	—	1	1	1	—	2	—	—	20
B	Penicillin, low dosage (800,000 units daily)	2	1	8	—	14	4	2	1	1	12	1	3	—	—	49
C	Penicillin, intermediage dosage (1,000,000 to 3,000,000 units daily)	2	4	39	1	6	1	3	2	—	4	3	2	1	—	68
D	Penicillin, high dosage (4,000,000 units daily)	1	1	23	—	15	4	1	6	—	9	2	1	—	1	64
E	Broad - spectrum antibiotics ..	1	4	4	—	6	2	—	—	1	2	3	3	—	—	26
F	Mixed antibiotics ..	1	4	7	—	16	2	—	2	—	2	1	2	—	—	37
	Total	7	14	84	1	68	14	6	12	3	30	10	13	1	1	264

TABLE V

Response of Fever to Treatment in 85 Patients Infected with Australis A or "Esposito"

Treatment Group[1]	Number of Patients	Total Duration of Fever (Days)			Duration after Treatment (Hours)			Day of Illness Treatment Commenced		
		Range	Mean	Standard Deviation	Range	Mean	Standard Deviation	Range	Mean	Standard Deviation
A	3	3 to 7	5·6	—	—	—	—	—	—	—
B	8	3 to 7	4·9	1·1	28 to 86	60·7	17·7	2 to 4	2·4	1·3
C	40	2 to 7	4·0	1·2	12 to 120	39·6	22·4	1 to 6	2·6	1·2
D	23	2 to 9	3·9	1·5	16 to 124	35·2	21·1	1 to 5	2·6	0·9
E	4	5 to 8	6·0	—	24 to 72	44·0	—	2 to 8	4·8	—
F	7	3 to 7	5·4	1·3	60 to 108	76·5	8·9	1 to 4	2·6	1·0

Standard errors of differences:

		Standard errors of differences:	
B–C	0·4	B–C	7·1
C–D	0·4	C–D	5·5
B–D	0·5	B–D	7·6

[1] See Table IV.

lowers the average duration of fever for that group; but it is evident that two of three untreated patients had total durations longer than six days, whereas only three of 71 who received penicillin had durations of that magnitude. In two of these three cases it is probable that the inclusion of the secondary rise in temperature may have given a falsely high value.

Australis B.—Sixty-eight patients infected with *australis B* are available for analysis. The illness of one of these (H.B., discussed above) differs so much in total duration from all others in the group that he has been excluded from the analysis. The response to treatment of the remaining 67 patients is set out in Table VI.

Eleven received no antibiotics; the average total duration of their illness was significantly longer than that of any other group. The intermediate and high penicillin dosage groups appeared to do equally well, and to recover significantly more quickly than the low penicillin dosage group. The figures are somewhat obscured by the small numbers in the intermediate dosage groups, and by the fact that these patients were treated comparatively late. The differences between the low dosage and high dosage groups are statistically significant for duration after treatment, but do not reach significance for total duration.

Other serotypes.—Smaller numbers of patients infected with the less common serotypes are available for study, and clear-cut differences cannot always be demonstrated. Thus patients infected with "Kremastos" showed little difference in total duration of fever between the three penicillin groups. The high dosage group had the shortest duration after treatment; but the average day on which treatment was

TABLE VI

Response of Fever to Treatment in 66 Patients Infected with Australis B

Treatment Group[1]	Number of Patients	Total Duration of Fever (Days)			Duration after Treatment (Hours)			Day of Illness Treatment Commenced		
		Range	Mean	Standard Deviation	Range	Mean	Standard Deviation	Range	Mean	Standard Deviation
A	11	5 to 10	7·4	1·4	—	—	—	—	—	—
B	14	3 to 10	5·5	2·1	28 to 164	66·6	38·5	2 to 6	3·1	1·2
C	6	3 to 8	5·5	1·5	12 to 64	39·6	18·5	3 to 7	4·6	1·7
D	15	3 to 7	4·6	1·6	18 to 64	36·9	13·0	2 to 5	3·4	1·2
E	6	5 to 6	5·2	0·5	30 to 96	60·3	25·5	2 to 5	3·2	1·2
F	15	3 to 8	5·5	1·4	22 to 122	77·3	35·7	1 to 4	2·7	0·9

Standard errors of differences:

		Standard errors of differences:	
A–B	0·7	B–C	12·8
A–D	0·6	B–D	10·7
A–E	0·5	B–E	14·6
B–D	0·7	D–E	10·9
D–E	0·5		

[1] See Table IV.

commenced was much later in that group. It may be stated that the response to penicillin of infections with the other serotypes appears to follow the pattern found with *australis A* and *australis B* infections; but the numbers concerned are too small for the results to be significant.

Day of Treatment.—The day of illness on which treatment was commenced introduces a variable which is susceptible to further analysis. The high and intermediate penicillin dosage groups of patients infected with *australis A* did not differ significantly in their response, and may therefore be considered together. This composite group is analysed in Table VII.

TABLE VII

Relation between Day on which Treatment was Commenced and Speed of Response in Australis A Infections Given High or Intermediate Penicillin Dosage

Day Treatment Commenced	Number of Patients	Total Duration of Fever (Days)		Duration of Fever, after Treatment (Hours)	
		Range	Mean	Range	Mean
1	4	2 to 4	3·0	28 to 86	57·5
2	27	2 to 7	3·4	12 to 120	39·7
3	20	3 to 5	4·2	16 to 60	34·1
4	8	4 to 9	5·2	18 to 124	40·1
5	3	5 to 6	5·6	16 to 28	22·6

Patients treated on the second, third and fourth days of illness responded in almost the same times. The averages for patients treated on the first and fifth days are based on very small groups. This may account for the divergence, but other factors may be operative. Thus some patients treated on the fifth day may have been about to recover without antibiotic assistance. Analysis of *australis B* infection treated with the higher penicillin dosages gives similar results, but the numbers are smaller and the figures therefore less significant. This suggests that, at least for patients treated on the second, third and fourth days of illness (who constitute three-quarters of the series), the duration of fever after treatment with these dosages of penicillin is independent of the day on which treatment is commenced.

It would seem, therefore, that the average duration of fever after treatment would be more reliable index of the relative values of rival regimes if it was estimated from patients treated only on the second, third, or fourth days of illness. Table VIII analyses the material from Tables V and VI in this way. It is evident that *australis A* and *australis B* infections show similar responses. The figures do not differ significantly from those in Tables V and VI.

Duration of Treatment.—There is no evidence in the present series that treatment of leptospirosis with penicillin should be continued for more than two days after the patient's temperature has fallen to normal. No patient relapsed whose treatment was stopped early, and a prolonged course of penicillin had no effect on the occurrence or duration of a secondary rise in temperature.

Discussion.—It seems well established that penicillin is leptospirocidal in concentrations of one unit per millilitre and higher, and in lower concentrations for some strains, and that it is leptospirostatic in concentrations between 0·03 and one unit per millilitre (Jennings, 1949; Alston and Broom, 1944), although some workers have considered it leptospirostatic at all effective concentrations (Chang, 1946; Rosenberg, 1951). Published work (Eagle *et alii*, 1949) suggests that the higher penicillin dosages used would produce a blood level within the leptospirocidal range in all cases, while the lower dosage would produce a blood level that would be leptospirostatic for most strains.

This can be correlated with certain features described in the present series. Thus the

TABLE VIII

Response of Fever to Antibiotic Treatment of Australis A and Australis B Infections Treated on the Second, Third or Fourth Days of Illness

Treatment Group[1]	*Australis A* Infections			*Australis B* Infections		
	Number	Average Total Duration (Days)	Average Duration after Treatment (Hours)	Number	Average Total Duration (Days)	Average Duration after Treatment (Hours)
B	8	4·9	60·7	13	5·2	63·3
C	36	4·0	38·4	3	4·6	49·0
D	19	3·9	36·5	10	3·7	35·4
E	2	5·0	56·0	5	5·0	63·0
F	6	5·8	79·3	14	5·6	76·8

[1] See Table IV.

similar responses to high and intermediate dosages of penicillin, and the slower response to the low dosage, could have been predicted from the differing mechanisms of action. Infections treated with bacteriostatic dosages of antibiotics have certain characteristics, notably a tendency to relapse if treatment is stopped early, and, as recovery depends on the development of the patient's immunological defences, a more rapid response the later treatment is commenced. That the action of penicillin should be equally rapid on the second and fourth days, and that no patient should relapse after treatment, tend to confirm the observation that penicillin, in the higher dosages, is indeed leptospirocidal.

Results of Treatment with the Broad-Spectrum Antibiotics

Twenty-six patients were treated with a broad-spectrum antibiotic without receiving penicillin. Chloramphenicol is the antibiotic usually employed in scrub typhus in this area; as the diagnosis between leptospirosis and scrub typhus is frequently difficult, the possibility that leptospirosis can be treated as effectively with chloramphenicol as with penicillin is of some importance.

Three *australis A* infections were treated with chloramphenicol and one with tetracycline. The average total duration of fever was longer than that found in the higher dosage penicillin groups, but treatment was commenced comparatively late, and the duration of fever after treatment was only a little longer (Table V). Three *australis B* infections were treated with chloramphenicol, two with oxytetracycline and one with tetracycline. The average duration of fever was significantly shorter than in the group of patients who received no antibiotics; the response to treatment appeared to be similar to that to low dosages of penicillin, and slower than that to the higher penicillin dosages. Infections with *icterohæmorrhagiæ* (one), *canicola* (three), "Robinson" (two), *medanensis* (one), "Kremastos" (two), "Szwajizak" (three), and "Celledoni" (two) were treated with chloramphenicol; one "Celledoni" infection was treated with erythromycin and one *canicola* infection with oxytetracycline. The results suggest that these antibiotics have a slower effect on the course of leptospirosis than the higher dosages of penicillin. This may, of course, be due to their different mechanism of action. It would be of greater importance to determine whether they are effective in preventing serious complications; but the present series is not large enough to permit any statement on that point.

Group F, in which both penicillin and one of the broad-spectrum antibiotics were used, is of importance in that most cases in the group represent the failure (or what the attending practitioner considered failure) of the antibiotic used initially. If a large number of the more severe cases in any other group were removed from analysis by inclusion in Group F, the average duration of illness in the remaining cases would be misleadingly low. This group therefore requires study as a possible source of fallacy in the conclusions drawn above. Seven *australis A* infections were treated with two antibiotics; two of these patients received an adequate penicillin dosage as initial treatment and became afebrile in sixty-eight and seventy-six hours. Inclusion of these figures in group C of Table V would not have materially altered the results. Fourteen patients with *australis B* received two antibiotics; two made such a rapid recovery that the reason for the giving of the second antibiotic is not clear, six received chloramphenicol initially, two received penicillin in low dosage, and four received penicillin in what would be considered adequate dosage. Table VI would not have been materially altered by the inclusion of these fourteen patients in the groups corresponding to their initial treatment. There is therefore no evidence that group F in any way invalidates the results obtained from study of the other groups.

CONCLUSION

The evidence presented here supports the previous statement (Doherty, 1955) that, among patients with leptospirosis in North Queensland, those who are treated with penicillin recover more rapidly than those who receive no antibiotic, and those who receive a high dose of penicillin more quickly than those who received a low dose. This conclusion depends on evidence from *australis A* and *australis B* infections, but other serotypes appear to behave similarly, so far as they have been observed. There is no evidence that increasing the dose above 2,400,000 units per day improves the results in *australis A* infections; this may be suggested as a suitable dose for future treatment. It remains to be seen whether dosage of this magnitude will lower the mortality in series from areas where the leptospiroses are less common than in North Queensland, and are therefore diagnosed at a later stage of illness.

SUMMARY

Of 273 patients with leptospirosis studied in North Queensland between July, 1952, and May, 1955, 266 had uncomplicated courses;

two became uræmic, and one of these also became grossly jaundiced; this patient and four others developed iritis, cyclitis or iridocyclitis in convalescence; one patient was proved to have leptospiral meningitis.

Details of treatment and response were available from 264. The two patients who became uræmic received no antibiotic during the initial febrile period of their illness.

Analysis of 85 cases of *australis A* or the closely related "Esposito" infection, and of 68 cases of *australis B* infection, showed that, for each serotype, the toal duration of fever and the duration of fever after treatment were less in patients given intermediate and high dosages of penicillin than in those give a low dosage.

Patients infected with *australis A* and treated with penicillin on their second, third or fourth days of illness responded in times not significantly different.

Twenty-six patients received one of the broad-spectrum antibiotics; analysis suggested that the response was inferior to that from higher dosages of penicillin.

ACKNOWLEDGEMENTS

The writer is indebted to the medical practitioners of North Queensland for their cooperation, to the Medical Superintendents of Cairns Base Hospital, Innisfail District Hospital and Gordonvale Memorial Hospital for permission to publish case histories of their patients, to Dr. W. Horsfall of the Commonwealth Health Laboratory, Cairns, for the liver function tests, blood urea estimations and cerebo-spinal fluid examination recorded, to Miss C. J. Ross and Miss M. L. Emanuel for their able assistance in the investigation of the patients, and to Dr. J. I. Tonge and the staff of the Laboratory of Microbiology and Pathology for the agglutination tests and the typing of the cultures.

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STUDIES IN FAT ABSORPTION

I. METHODS AND RESULTS IN CONTROLS AND IN PATIENTS WITH STEATORRHŒA[1]

PATRICIA J. CROWE, B.Sc.,[2] AND C. R. B. BLACKBURN[3]

From the Clinical Research Unit[4] and Gastroenterology Unit,[5] Royal Prince Alfred Hospital, Camperdown, New South Wales

Abnormalities of fat absorption in humans are usually studied by plotting absorption curves in the blood after test doses of fat or vitamin A have been given by mouth or by the balance method in which the fat intake and the fat excretion are determined. Usually the fæces only are analysed, as the urinary excretion of fats is negligible. In the latter method apparent fat absorption is measured, because no allowance is made for synthesis by bacteria or for excretion into the gastro-intestinal tract.

In general, quantitative methods based on the excretion of fat in the stools require some form of fat balance. The full balance method is undoubtedly the best; and to carry it out both the diet and the stools are analysed for fat content and the balance is determined over a period of three to six days. A weighed diet is given to the patient, an exact duplicate is kept for analysis, and all diet residues are weighed, analysed and subtracted from the duplicate diet. Carmine capsules are used to mark the stools at the beginning and the end of the study period. This full balance technique is a very useful tool for investigations of fat absorption requiring more accuracy than that needed to establish a diagnosis of steatorrhœa. It can be carried out only where the facilities of a metabolic unit are available for the collection and analysis of diet and fæces and for the close supervision of the diet.

A variation of the full-balance method eliminates the analysis of diet by using food composition tables to calculate the fat content of weighed diets. Otherwise the same technique is used.

A third variation of the balance method is often used, because balances requiring weighed diets are impracticable in general hospital wards, as diet supervision is difficult. Patients receive an ordinary unweighed ward diet, the fat content of which will always be less than 150 grammes per day as long as excess fat is not taken—for example, excess cream or butter—and their stools are marked at the beginning and end of the study period of three to four days. This balance method is based on the observation that the amount of fat in the fæces in normal subjects is relatively constant and is independent of the dietary intake provided it does not exceed 150 grammes per day (Cooke *et alii*, 1953).

Some investigators (Anderson *et alii*, 1952; French, 1952) prefer to analyse twenty-four hour stool specimens so as to follow the daily fluctuations. Daily analyses of fat in the fæces are obviously more time-consuming than the single analysis which is required when carmine is used to mark a four-day collection period. Constipation may interfere with the daily collection of a stool for twenty-four hour analysis, but makes no difference if stool markers are used over a three-day to four-day period.

Qualitative methods for evaluating fat absorption have been most frequently used in the past. These tests are performed on random specimens of stool and do not represent any particular portion of the daily output of fat in the fæces. The most common method is to extract the dried fæces with ether and to express the extracted fat as a percentage of the dried weight of the fæces. Kamer *et alii* (1949) showed that ether extracts not only fats but also other ether-soluble non-fats, thus giving high estimates. Comparison of results obtained by this method with those obtained by the more reliable fat-balance method showed little correlation (French, 1952). Another very rough qualitative method is the microscopic examination of fæces with the

[1] Received on September 27, 1955.

[2] Dietitian to the Clinical Research Unit.

[3] Director, Clinical Research Unit, Royal Prince Alfred Hospital.

[4] Supported by the National Health and Medical Research Council.

[5] Supported by an anonymous donor.

use of Sudan III as a staining agent. Reliable quantitative methods are now available and should replace the older qualitative methods.

Of the quantitative balance methods described above, two have been chosen as particularly suitable for our needs as diagnostic tests for steatorrhœa. The first method, a partial balance, in which calculation was substituted for analysis of the fat content of weighed diets, was used only on patients admitted to the Clinical Research Unit. The second method—fæcal fat analysis on patients receiving unweighed ward diet—was used to enable a diagnosis of steatorrhœa to be made without transferring the patient to the Clinical Research Ward.

METHODS

The usual length of the study period was three to four days. Weighed diets were supplied by the hospital diet kitchen, and the fat content was calculated from the food composition tables of Osmond (1948) and of McCance and Widdowson (1940). The stools were collected directly into cardboard containers. At the conclusion of the study the fæces were mechanically mixed with water in a macerator and made up to a suitable volume, and an aliquot of the fæcal suspension was analysed by a fatty-acid method of Kamer (1949), modified by the use of an aliquot of the fæcal suspension instead of a weighed amount of fæces. Carmine capsules were given to the patient at the beginning and end of the study period to mark the stools, all stools were saved for analysis after the appearance of the first carmine marker, and the collection was continued until the appearance of the second carmine marker and then stopped. All stools containing the second marker were discarded. Carmine was preferred to charcoal as a marker, as experience of both has shown that carmine is easier to recognize.

RESULTS

Patients upon whom fat balance studies were carried out have been classified either as controls or as having the malabsorption syndrome. The control group consists of patients who were considered to show no evidence of malabsorption in their history, on physical examination or in the results of tests such as X-ray examination of the small bowel and oral glucose tolerance tests. The commonest reason for investigating patients in the control group was diarrhœa, and the final diagnoses included ulcerative colitis *anorexia nervosa*, duodenal ulcer and aplastic anæmia. The diagnoses in the malabsorption group were supported by the physical examination and history in every case, and by the results of X-ray examination of the small bowel and oral glucose tolerance tests in the majority of them. The results of 52 fat balance studies on 40 patients are shown in Table I.

Method A refers to the partial balance technique with the use of weighed diets of calculated fat content, and hence, the results can be expressed as percentage absorption of intake. In Method B the unweighed diets are assumed to contain less than 150 grammes of fat per day, and the results are expressed as grammes of fat in the fæces per day.

DISCUSSION

The values for fæcal fat in grammes per day in the control group for Method A and Method B were 2·6 (standard deviation 1·77) and 2·53 (standard deviation 0·8) respectively; these agree well with normal values published by other workers, which are set out in Table II.

The absorption in the control group (Method A) was always greater than 90%, which also agrees with the accepted value in normal subjects.

TABLE I

Results of Analysis of Fat in Fæces from Controls and Patients with Malabsorption.

Method	Number of Patients	Number of Analyses	Fat Intake (Grammes per Day)	Fat in Fæces (Grammes per Day)	Absorption
A	Control 12	13	68 average, 40 to 97 range	2·6, S.D.[1] 1·77, 0·9 to 6·2 range	96% average, 92% to 98% range
	Malabsorption .. 4	5	68 average, 31 to 101 range	16·3 average, 9·8 to 27·0 range	68% average, 12% to 89% range
B	Control 18	19	Less than 150	2·53, S.D.[1] 0·8, 0·9 to 4·2 range	—
	Malabsorption .. 7	15	Less than 150	43·6 average, 8·3 to 85·5 range	—

[1] Standard deviation.

In the malabsorption group, both methods being used, the average fat contents of fæces in grammes per day were 16·3 and 43·6 respectively. In fæces from those patients in whom steatorrhœa could be expected on clinical grounds, the lowest value was 8·3 grammes per day; this was significantly higher than any value in the control group. The individual diagnoses and the fat content of the fæces from patients in the malabsorption group are shown in Table III.

TABLE II

Results of Analyses of Fat in Fæces from Normal Subjects

Investigator	Number of Subjects	Fat Intake (Grammes Day)	Fæcal Fat (Grammes per Day)
Annegers (1948) ..	40	93 to 168	3·91 (S.D.[1] 1·01)
Fourman (1948) ..	—	70	2·88; upper limit, 5·7
Wollaeger (1947) ..	—	102	4·1 (S.D.[1] 1·5)
Cooke (1953) ..	48	50	2·7 (S.D.[1] 0·95)

[1] Standard deviation.

TABLE III

Diagnoses and Results of Analyses of Fat in Fæces from Patients in Malabsorption Group

Diagnosis	Number of Patients	Fæcal Fat (Grammes per Day)
Idiopathic steatorrhœa ..	3	(i) 23·3; (ii) 11·4; (iii) 13·3
Whipple's disease	1	61·0 (Average of nine determinations)
Biliary cirrhosis	1	10·8
Ileo-colitis	1	8·6
Lymphosarcoma	2	(i) 9·8; (ii) 19·5 (average of two determinations)
Cœliac disease	1	21·5 (average of two determinations)

In six cases, repetition of the test showed good reproducibility of results. Three patients, respectively suffering from Whipple's disease, cœliac disease and lymphosarcoma, showed persistent steatorrhœa on repeated tests. In the control group, a patient with ulcerative colitis and a dwarfed boy with congenital heart disease and normal fæcal fat content underwent repeated tests with consistent results.

Another patient, who had a macrocytic anæmia in association with steatorrhœa, was treated with vitamin B_{12}. The anæmia responded and the steatorrhœa disappeared, as indicated by two consistently normal results from fæcal fat analyses.

There has been no instance in this series of a patient with a high fæcal fat content who showed no clinical evidence of the malabsorption syndrome; but the reverse findings have been recorded. Four patients have been studied by the carrying out of a single determination of the fæcal fat content. The clinical and radiological features in these patients suggested the malabsorption syndrome, but the values for fæcal fat were well within the normal limits. All patients had deficiency patterns in X-ray films of their small bowel, and all had histories suggestive of the malabsorption syndrome. The fat contents of fæces in grammes per day were 3·3, 1·2, 3·0 and 3·4 respectively—that is, they were within the range of the control group. Unfortunately it has not been possible to follow these patients since their discharge from hospital, so that their subsequent course is unknown and the fæcal fat estimations have not been repeated.

CONCLUSION

Both methods of studying fat balance described are reliable means of demonstrating normal or abnormal fat absorption. The shorter method, analysis of the fat content of fæces only, has been shown to give the same information as the method which requires calculation of weighed diets to enable results to be expressed as percentage absorption. The shorter method has the advantage of being simpler, and therefore it enables patients to be studied in general hospital wards.

SUMMARY

Quantitative and qualitative methods of studying fat absorption have been discussed.

The techniques in current use are described, and the results of fat absorption studies on patients receiving standard ward diets, weighed or unweighed, are presented and discussed.

The normal fat content of fæces was found to be 2·6 grammes per day (standard deviation 1·7).

It is concluded that full fat-balance studies are unnecessary for the detection of steatorrhæa, and that the results of estimation of the fat content of the fæces is a reliable indicator of steatorrhœa.

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STUDIES IN FAT ABSORPTION

II. ORIGIN OF FAT IN FÆCES[1]

PATRICIA J. CROWE, B.Sc.,[2] C. R. B. BLACKBURN,[3] M. L. MASHFORD[4] AND C. S. H. REED[5]

From the Clinical Research Unit[6] and Gastroenterology Unit,[7] Royal Prince Alfred Hospital, Camperdown, Sydney

INVESTIGATIONS of the origin of fat in the fæces of normal humans have produced conflicting views on whether such fat is derived mainly from endogenous sources or from unabsorbed dietary fat. It is generally agreed that bacterial synthesis, desquamated cells of the intestine and bile contribute a small proportion of the total amount of fat. Norcia and Lundberg (1954), working on rats, consider that endogenous fat is derived from bacterial synthesis, a view that receives some support from the occasional response of some patients with steatorrhœa to the oral administration of anti-bacterial therapy (Frazer, 1955).

Wollaeger *et alii* (1947) concluded that dietary fat was the major factor in determining the amount of fat in the fæces. Increases in the dietary fat intake of up to 350 grammes per day were reported to result in significantly increased amounts of fat in the fæces. These workers also studied the data in the literature, and were able to prepare a diagram that clearly showed that as the fat intake increased, the fæcal fat content increased.

The results of investigations of fæcal and plasma lipids in two normal humans by Wollaeger *et ali* (1953) are of interest, because the subjects were studied while they were receiving a lipid-free diet after a period on a general mixed diet. During the lipid-free period there was a pronounced drop in the average fæcal lipid output from 7·7 to 1·5 grammes per day, due mainly to decrease fatty acid excretion from 4·3 grammes to 0·43 gramme per day. The composition of the fatty acids was found to vary from period to period, as shown by melting-point determinations and the degree of unsaturation of the acids. Since lipids continued to appear in the fæces during the ingestion of the lipid-free diet, without a corresponding fall in plasma lipids, the fatty acids were considered to be the unabsorbed residue of all the fatty acids which enter the intestinal tract by secretion, desquamation, bacterial synthesis and ingested foods, the major portion being derived from the last-mentioned source. These investigators disagree with the hypothesis that most of the fatty acids found in the fæces are excreted into the intestine, because this theory provides no satisfactory explanation for the abrupt reduction in the quantity of fatty acids in the fæces when fat was excluded from the diet. The theory of secretion does not explain the difference in composition of fatty acids during the control and lipid-free periods.

However, the results of earlier studies in dogs, by Sperry (1926) and Sperry and Bloor (1924), suggested to them that fæcal lipid was to a large extent derived from excreted material rather than from unabsorbed dietary fat. This hypothesis was based on their observations that changes in the amount and character of lipid in the food did not influence the amount or composition of the fæcal lipids.

These conclusions were considered by Annegers *et alii* (1948) to apply to normal humans, as variations of the dietary fat intake from 93 to 150 grammes per day did not appreciably influence the amount of fat in the fæces of 40 normal humans.

Cook (1952), after reviewing the available evidence on the source of fæcal lipids in normal humans, concluded that the greater part of the fæcal lipid was secreted by the intestinal walls, although no specific glands comparable to the sebaceous glands of the skin have been described. He based this conclusion on the evidence that the fæcal lipid was relatively constant in amount and composition, and that Popjak and Beeckmans (1950) had shown the

[1] Received on December 1, 1955.
[2] Research dietitian.
[3] Director.
[4] Medical Board Fellow in Medicine.
[5] Registrar.
[6] Supported by the National Health and Medical Research Council.
[7] Supported by an anonymous donor.

intestine to be metabolically active in the synthesis of lipids, including cholesterol.

Angevine (1929), using isolated loops of intestine in dogs, showed that the jejunum and ileum secreted a fatty fluid of constant composition, which was unaltered by changes in the fat content of the diet. Later work by Sperry and Angevine (1932) on dogs with fistulæ of lower part of the ileum, and receiving a lipid-free diet, demonstrated a larger excretion of lipids from the small intestine than had previously been found in the fæces under similar dietary conditions. At autopsy, the defunctioned colon was found to contain a fatty substance. As there was a possibility that, in the normal dog, the intestinal contents were delayed by the ileo-cæcal valve sufficiently long to permit local absorption, these workers performed further experiments on dogs with fistulæ of the cæcum and normal ileo-cæcal valves. The results of these experiments satisfied them that the observed increases in fat excretion from dogs with ileostomies were not due to alteration in function of the ileo-cæcal valve. They concluded that there was absorption and probably some secretion of lipids in the colon.

A study of three humans with presumably normal absorption, receiving fat-free diets, was reported by Lewis and Partin (1954). The average amount of lipid in the fæces was 2·0 grammes per day, which the authors interpret as being evidence for the intestinal secretion of lipids.

It is suggested by Cook (1952) that fæcal lipid serves specific functions in the intestine, both as a means of excretion of unabsorbable lipids and as a conditioning substance for the intestine. He quotes as evidence in support of the latter function the increase in fæcal fat after stimulation by food as reported by Walker (1949), who showed that the effect of increasing the fibre content of fat-poor diets of Bantu natives was to increase the fat content of the fæces to a small degree.

In patients known to have defective fat absorption, as in the sprue syndrome and cœliac disease, raising of the dietary intake of fat usually causes an immediate increase in the fæcal fat excretion. Brain and Stammers (1951), studying patients with post-gastrectomy steatorrhœa, and Comfort *et alii* (1953), studying patients with the sprue syndrome, showed that raising the fat intake from 50 to 100 grammes per day increased, but did not double, the fat in the fæces. In one of the cases described by Comfort, a reduction of the fat intake from 100 to 4·2 grammes per day resulted in a decrease of the amount of fat in the fæces from 65·4 to 14·2 grammes per day, and this decrease could not be attributed to any change in the state of the disease. Similar evidence of a strongly negative fat balance during a very low dietary intake of fat has been reported in a patient with idiopathic steatorrhœa, who ingested a diet containing 3·0 grammes of fat per day, but whose average fæcal fat output was 13·6 grammes per day (Cooke *et alii*, 1953). Jiminez-Diaz *et alii* (1953) also reported several patients with sprue-like enteritis who were in strong negative fat balance while on daily intakes of six or thirty grammes of fat. He advances the theory that all the fæcal fat in his patients was derived from intestinal secretion, and none from unabsorbed food. He did not explain the decrease in fæcal fat content to normal limits observed in six of thirteen patients when their diet was increased from 30 to 130 grammes of fat per day.

In 1950, Weijers and Kamer showed that in patients with cœliac disease there appeared to be either a specific failure to absorb saturated fatty acids or an actual excretion of saturated fatty acids in excess of the dietary intake. The latter explanation was preferred by Weijers and Kamer (1953), as they showed that children with cœliac disease, maintained on a diet containing gluten but no fat, passed six to 10 grammes per day of saturated fatty acids in their fæces. The presence of excess endogenous fat may explain the findings of Comfort *et alii* that doubling the dietary intake does not double the amount of fat in the fæces. However, any defect which prevents normal absorption of dietary fat may also prevent the normal reabsorption of fat from the bile and other endogenous sources, leading to an increased amount of fat in the fæces (French, 1955).

In the present investigation, two patients with steatorrhœa, J.S. and H.W., have been studied to determine the origin of their fæcal fat. One of them was suffering from lymphosarcoma and had been exposed to considerable abdominal irradiation; the other was thought to be suffering from Whipple's disease. They were both given diets containing increasing amounts of fat, and duplicates of these and the fæces produced during each period were analysed. Brief histories of the two patients are given later in this paper.

METHODS

The balance studies on J.S. and H.W. were divided into three consecutive six-day periods and one period of three days. In the case of

TABLE I

Results of Fat Balance Studies on Patient J.S.

Period	Days	Diet (Grammes per Day)	"Ol Vita D" (Grammes per Day)	Diet Residue *plus* Vomitus (Grammes per Day)	Intake (Grammes per Day)	Fæces (Grammes per Day)	Balance (Grammes per Day)
I	6	1·5	0·34	0·8	1·0	3·5	−2·5
II	6	11·2	0·34	0·4	11·1	3·9	+7·2
III	6	36·6	0·34	0·8	36·1	9·9	+26·2
IV	3	0	0	0	0	0·7	−0·7

J.S., the last-mentioned period followed immediately after biopsy of his cæcum, during which time he was wholly maintained by lipid-free food given parenterally. The three-day period in the case of H.W. followed immediately after the commencement of therapy with 10 milligrammes of folic acid per day.

The diets were supplied by the diet kitchen together with exact duplicates, and the latter were analysed for fat content. All diet residues and vomitus were collected and the fat content was estimated. Fæcal collections and fat estimations on all materials were performed as described in the first paper in this series (Crowe and Blackburn, 1956).

Diets

For the first period both patients received diets of very low fat content, which consisted of dried skim-milk powder, cereals, bread, fruit, and a small amount of fish and chicken.

In the case of J.S. the basic diet was supplemented during periods II and III by increasing amounts of meat and "Sao" biscuits. In period IV he took nothing by mouth, but was maintained with fluids given intravenously.

H.W.'s diet included an additional 10 grammes of butter and a small portion of meat each day during period II. During periods III and IV the diets given were identical, and contained an additional 20 grammes of butter and increased amounts of meat each day.

RESULTS

The results of the fat balance studies on the two subjects are shown in Tables I and II. The results indicate that both patients were in negative fat balance to the extent of 2·5 and 1·7 grammes per day respectively while on a very low intake of fat during period I. During this period both patients vomited and frequently passed copious liquid stools.

As the dietary fat intake was increased to approximately 38·0 grammes per day, the fæcal fat output increased, although more fat was retained. The general condition of both patients improved during the study, and their diarrhœa and vomiting decreased; indeed, during periods III and IV, H.W. was extremely constipated, but her steatorrhœa increased.

J.S. was maintained entirely on glucose and saline given intravenously in period IV (Table I), which was immediately post-operative. His fat balance became negative to the extent of 0·7 gramme per day, though his pre-operative fat balance was +26·2 grammes per day in period III. Folic acid was administered to H.W. in period IV (Table II), but it was without effect on the degree of steatorrhæa.

DISCUSSION

The patients in this study had secondary steatorrhœa, which might, it could be argued, have been based upon different mechanisms in each case, and different mechanisms from that of so-called idiopathic steatorrhœa.

TABLE II

Results of Fat Balance Studies on Patient H.W.

Period	Days	Diet (Grammes per Day)	"Ol Vita D" (Grammes per Day)	Diet Residue *plus* Vomitus (Grammes per Day)	Intake (Grammes per Day)	Fæces (Grammes per Day)	Balance (Grammes per Day)
I	6	2·1	0·34	0·4	2·0	3·7	−1·7
II	6	19·3	0·34	0·05	19·6	10·9	+8·7
III	6	38·3	0·34	0	38·6	18·8	+19·8
IV	3	38·1	0·34	0	38·4	20·0	+18·4

However, it is considered that the conclusions to be drawn from the data are consistent with the picture of the whole problem of steatorrhœa which is outlined in this paper.

The fæcal fat is obviously fat which has escaped absorption. In the normal individual on an average diet this is of endogenous origin, since the amount of fat in the stools changes very little when the fat intake is increased from very low levels to 150 grammes or more each day. A part of this is derived from the bacterial flora of the bowel and from desquamated mucosal epithelium, but this is considered by most authors to be of minor importance.

Angevine (1929) constructed a Thirty-Vella fistula in each of two dogs by isolating a loop of bowel and bringing each end through separate abdominal wall wounds and restoring the continuity of the bowel by an end-to-end anastomosis. In one case the fistula was ileal and in the other jejunal. Angevine demonstrated the secretion of a fat-containing fluid in both, and found no difference in amount in the different sites. Sperry and Angevine (1932) found in dogs with ileal fistulæ that the defunctioned colon accumulated a fat-containing material. It is assumed that similar widespread secretion takes place in the human; indeed, Doubilet *et alii* (1937) showed that the ileum secreted a fatty fluid.

The fat secreted by the intestine differs little from the readily absorbed dietary fat, and therefore the concentration of lipids at any level represents a balance between secretion and absorption throughout the whole bowel proximal to that level. The fæcal lipid of a person receiving nothing by mouth must represent fat secreted distal to an adequate absorbing surface. This resting state may be modified by the introduction of food into the intestine. Walker (1949) reported some data which may be adduced in support of this view; he found small increases in the fat excreted by normal persons taking large amounts of fibre in their diet. This may be explained on the physical basis of greatly increased bulk of intestinal contents. Our patient J.S. strikingly illustrates the effect of the entry of food into the intestine. When he was maintained by the intravenous administration of fluids only and received nothing by mouth, his fæcal fat output reached the very low figure of 0·7 gramme per day; but when a diet giving him only 1·0 gramme per day was eaten, his fæcal fat output was 3·5 grammes per day. It is reasonable to suppose that the difference was largely due to the presence of food in the alimentary tract which stimulated increased secretion, if only for the lubricating function suggested by French.

There is little evidence that increased dietary fat intake increases intestinal secretion. Indeed, Angevine's work with dogs failed to show any change in secretion when the fat content of the diet was increased from low to moderate and then to high levels. He worked with isolated loops of bowel, and so he did not exclude a local action on the bowel wall.

If the absorbing bowel is considered to consist of a finite series of segments, which for clarity will be assumed to be of identical function, then each segment will have a capacity to absorb fat limited by a maximum absorptive capacity and also influenced by its absorptive efficiency. The latter will be governed by many factors, including the nature of the chyme, the time of its contact with the mucosa of the segment concerned and the state of the mucosal transport mechanisms themselves. In other words, a given percentage of the fat in the chyme will be absorbed up to a maximum absolute figure in a given time, when the absorptive mechanism will be saturated, and any further increase in the fat content of the chyme only leads to an increasing concentration being presented to the succeeding segment. If the fat load was increased, successive segments would be absorbing maximally until the whole bowel was unable to increase its total absorption. If a normal person is given increasing amounts of fat in his diet, there is only slight increment in stool fat content as the intake rises—indeed, some authors deny any increase. However, if enough fat could be eaten without producing nausea or altered bowel function, the maximum absorptive capacity of the whole bowel would be exceeded and fat of undoubted dietary origin would appear in the fæces.

In the normal subject then, fat is regarded as entering the bowel from the stomach (dietary) and along its length (secreted). This content is submitted to absorptive action during its passage through the bowel, and the fat finally excreted is the small amount, usually three to five grammes per day, which has escaped absorption. With normal dietary loads, the exogenous fat has been removed from the bowel lumen before it reaches the distal part of the intestine, and the fæcal fat is of endogenous origin. With excessive loads, fat of mixed origin is excreted.

In abnormal states due to disease or bowel resection, the amount and behaviour of the intestine determine the amount and origin of the fæcal fat. With a high efficiency but

decreased maximum absorptive capacity, as in the case of surgical ablation of a considerable length of intestine, little change from normal might be expected until high fat loads were given. This was found to be the case in one patient studied by us, in whom an unknown length of ileum and colon was removed in the repair of a strangulated ventral hernia. She excreted normal amounts of fat on diets containing up to 30 grammes per day; but on a normal diet estimated to contain about 70 grammes per day, she excreted 8 grammes of fat daily. However, if the absorptive efficiency is depressed in the idiopathic form of steatorrhœa, as proved by vitamin A absorption tests and chylomicron counts, a steady rise in fæcal fat levels may be expected as the fat intake is increased. If the absorptive maximum is not seriously impaired, there should be no sharp rise in excretion even when higher intakes are reached.

Both of our patients had fæcal fat contents within normal limits when they ate diets containing one to two grammes of fat per day, and patient J.S. excreted normal amounts of fat even when his intake rose to 11·1 grammes daily. Both had greatly increased excretion when their daily fat intake was increased further, and the higher the intake the greater the amount excreted. However, the relationship was not linear, and the greater the amount of fat consumed the greater the absorption, resulting in an increasingly positive fat balance within the limits of the experiment. This is a common finding in steatorrhœa, although Jiminez-Diaz *et alii* (1953) reported some patients whose fat excretion declined sharply when the dietary fat intake was increased from 30 to 130 grammes per day.

Our data are best explained by the assumption that secretion of fat into the fasted intestine is minimal, but is increased by the introduction of food. It may also be increased by factors at present unidentified, but it does not seem to depend significantly upon the dietary fat content. The fæcal fat is of mixed origin, and the proportions of dietary and secreted fat depend on the level of intake in the particular patient concerned. Thus on a fat-free diet it must be wholly endogenous, whereas in a severely affected patient on a fat-rich diet it may be 90% exogenous in origin. In patients with steatorrhœa impaired absorption is the major causative factor and this affects both dietary and secreted fat.

The clinical implication of our data supports the conclusion that the major reason for limiting the fat intake is that the patient is less inconvenienced by the bulk of his stools. On the other hand, eating more fat leads to greater fat absorption and therefore a more favourable caloric intake. When treating a patient it is wise to increase the daily fat intake slowly to as high a level as is compatible with reasonable comfort. Difficulties of stabilization arise as a result of the spontaneous variations that occur in the degree of steatorrhœa and diarrhœa.

Reports of Cases

J.S., a male patient, at the time of the present study was aged twenty-eight years. Six years earlier, by lymph-node biopsy, the diagnosis of follicular lymphoblastoma had been made, and he had been given a number of courses of deep X-ray therapy to areas including the abdomen. He had had bouts of diarrhœa since the inception of his illness, but this became much worse three and a half years later, after treatment with triethylene melamine. Some seven months after this, steatorrhœa was proved to be present when the average daily fat excretion on an average ward diet was found to be 9·5 grammes. At that time only minor abnormalities of the small bowel were revealed by X-ray examination. He was admitted to hospital the following year with an acute exacerbation of diarrhœa, with dehydration and loss of muscle mass. The study reported here was carried out during this period in hospital. At the conclusion of the third study period, an exploratory laparotomy was performed to exclude a local small bowel lesion as the cause of his steatorrhœa, and a biopsy of his cæcum was taken. The fourth study period was immediately post-operative. During the first and second periods he was given 25 grammes of salt-poor human albumin per day intravenously in connexion with other investigations. Phthalylsulphathiazole, two grammes every four hours, was administered continuously until laparotomy, and subsequent to this he was given 0·5 gramme of streptomycin twice daily by intramuscular injection.

H.W., a female patient, was aged forty-nine years at the time of the study. She has a history of periodic attacks of arthritis commencing at the age of twenty-nine years and continuing up to the present, but she has little or no permanent stiffness of the joints. She had first been troubled by diarrhœa nine years before this admission to hospital, and two years after the commencement of this symptom she was submitted to exploratory laparotomy. Tissue was removed at this time, and reported as showing changes consistent with Whipple's disease. Steatorrhœa had been demonstrated one year preceding the present study, when she was found to excrete 80 grammes of fat per day when eating a normal ward diet containing less than 150 grammes of fat per day. During this study she was given calcium lactate and vitamin *D* by mouth, and during the last period 10 milligrammes of folic acid were administered by mouth each day.

Summary

Two patients with secondary steatorrhœa were studied by the fat balance technique over four periods, with the object of observing the effect of increasing fat intakes on fæcal fat excretion.

Both patients excreted normal amounts of fat when eating diets almost free from fat, but an increased intake resulted in increased excretion.

In one patient the fat excretion was determined whilst he took no food by mouth, and his fæcal fat excretion was much less than when he ate a diet very low in fat.

Some aspects of the physiology of fat absorption are discussed, and the data reported have been examined in the light of these concepts.

ACKNOWLEDGEMENTS

We should like to thank Dr. S. J. M. Goulston for permission to study the patient H.W.

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CONTROL OF BODY FLUID VOLUME IN MAN : FURTHER OBSERVATIONS ON INTAKE, OUTFLOW AND VOLUME OF BODY FLUID[1]

T. E. Lowe[2]

From the Baker Medical Research Institute and Alfred Hospital Clinical Research Unit, Melbourne

Arising from observations concerning the control of body fluid volume in man and animals (Lowe, 1950, 1951, 1952, 1953; Lowe and Sayers, 1952; Fraser and Lowe, 1954; Fowler, 1955*a*, 1955*b*; Hamilton, 1955) and experiences with an hydraulic model of this system, an hypothesis which relates inflow, outflow and volume of fluid stored has been propounded (Lowe, 1955).

In this paper some of the implications of this hypothesis are examined, predicted behaviour is compared with that observed in patients, and the possible nature of the relationships between inflow, outflow and volume are indicated.

Material

The observations recorded are selected from a series of 265 patients, whose daily intake and output of fluid and body weight have been recorded under standardized conditions (Lowe, 1951).

The daily periods of observation were from noon to noon except in a small number of cases early in the series, in which the period was from midnight to midnight.

The patients suffered from a considerable variety of conditions, including congestive cardiac failure, hypertension, nephritis, nephrotic syndrome, endocrine disorders.

Hypothesis

The hypothesis relating inflow, outflow and body fluid volume which has been proposed (Lowe, 1955) considers that the body fluid is a solvent (water) containing a variety of solutes, and that that fluid is stored in an "open" storage system through which there is a continuous flow. Within the storage is a receptor mechanism (or mechanisms), sensitive to at least two aspects of the fluid stored, which controls both the inflow and outflow of fluid. It was suggested that two of the aspects of the fluid storage to which the receptor mechanism is sensitive are change in volume and osmotic pressure of some portion of the storage.

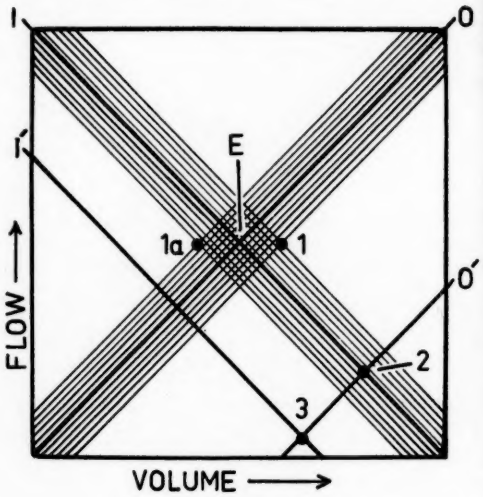


Figure I

Graph showing changes induced in inflow (I) and outflow (O) by changes in volume of the hypothetical system. Changes in flow induced by changes in the second controlling factor are indicated by the family of lines parallel to I and O. E indicates one equilibrium point at the intersection of I and O lines. I′ and O′ indicate lines of depressed inflow and outflow function. 1, 1*a*, 2 and 3 indicate abnormal equilibria which are considered in the text

From study of the hydraulic analogue of this system it was thought that its behaviour could be represented diagrammatically as in Figure I. If the receptor mechanism is considered to be sensitive to only one factor (for example,

[1] Received on November 23, 1955. Part of the expenses of this investigation were defrayed by a grant from the National Health and Medical Research Council.

[2] Director of the Baker Medical Research Institute and the Alfred Hospital Clinical Research Unit, Melbourne.

volume of the system) then the lines I (inflow) and O (outflow) indicate the behaviour when volume changes exercise a linear control over flow. If a second control is postulated (for example, osmotic pressure) and there is a linear relationship between this second control and flow, then instead of the single lines I, O there will be families of parallel lines. In a three-dimensional graph these would be represented by intersecting planes. Equilibrium points (E) exist where corresponding flow lines intersect.

In view of the fact that the body fluids are contained in a complex compartmented structure, some form of transfer mechanism is necessary for the distribution and conveyance from inflow to outflow points. Such a mechanism is provided by the circulatory system, and is probably influenced by all factors affecting partition of the fluid and any agents, such as protein molecules, which may act as water carriers.

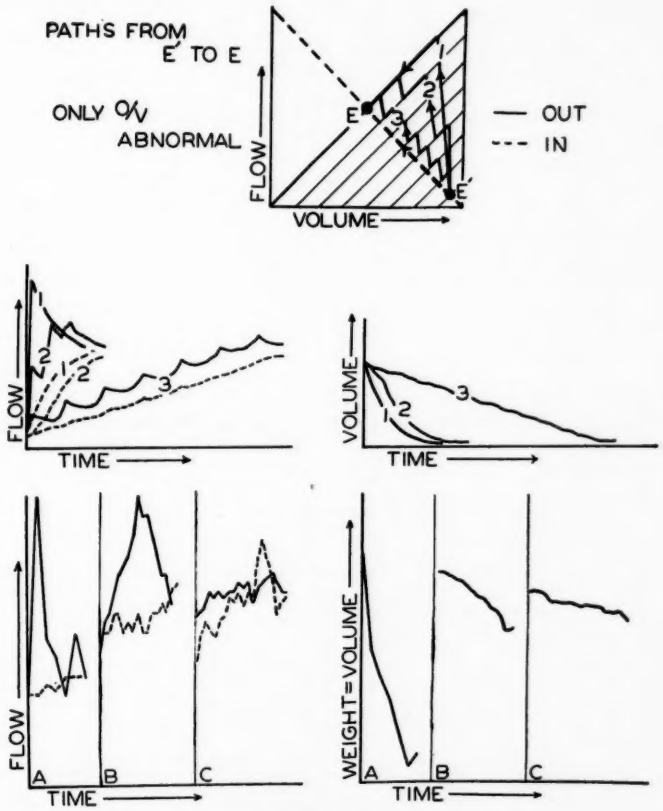


FIGURE II

Graphs showing, in various ways, recovery pathways of the system from an abnormal equilibrium (E') (contrast 2, Figure I). In this case only the outflow-volume relationship is abnormal. Path 1 indicates very rapid restoration of the O/V relation to normal, paths 2 and 3 indicate stepwise returns to normal. A, B and C indicate observed changes in inflow, outflow and volume in three patients for comparison with the predicted paths 1, 2 and 3

Inherent in the hypothesis as applied to the intact body is the concept that the inflow mechanism must include some part of the transfer mechanism. The lines I and O in Figure I therefore indicate the behaviour of the compound mechanisms.

When a system such as this is disturbed from equilibrium, it will return to an equilibrium

point, but would take infinite time to reach it. This difficulty occurs in other physiological problems (Wesson *et alii*, 1948) and, in the living organism, it appears that as the equilibrium point is approached such a system breaks into random oscillation about that point. The equilibrium zone is then reached in finite time.

ANALYSIS

Of the many possible disturbances of this proposed system three will be examined in detail. The first is the sequence of events in the return to normal from an equilibrium in which the outflow to volume relationship (O/V) alone is depressed (Figure I, 2). The second is the recovery from an equilibrium due to abnormal osmotic pressure impressed upon the system (Figure I, 1, 1*a*). Here O/V and I/V are altered in opposite directions. The third is the progression from the normal equilibrium to one in which both inflow (I/V) and outflow (O/V) to volume relationships are depressed, and subsequent recovery from that situation (Figure I, 3).

Depression of Outflow to Volume Relationship

Depression of the outflow to volume relationship is illustrated in Figure II, which shows a series of lines parallel to O (see Figure I), on which for a given volume the outflow is less than normal, and a new equilibrium point (E′) at a greater than normal volume. If in some way the outflow function is suddenly restored to normal, the system is out of equilibrium, and both the inflow and outflow will progress along the lines 1 to the normal equilibrium E at normal volume.

Several ways of recording this progress are possible, and in Figure II two of them, flow against time and volume against time, are indicated.

The graph A of Figure II shows the changes in inflow, outflow and volume plotted against time in the case of a patient recovering rapidly from congestive cardiac failure following on a hæmopericardial effusion. In this case recovery starts immediately after withdrawal of the pericardial fluid which was causing tamponade.

If recovery from the abnormal equilibrium point is not sudden but takes place in steps, few (Figure II, 2) or many (Figure II, 3), then the changes in inflow, outflow and volume will be as indicated. In Figure II, B and C are observations made on patients recovering from congestive cardiac failure when treated by bed rest alone (Lowe, 1950).

It will be noted that one feature of the behaviour in these three situations is that in the initial recovery period the changes of inflow and outflow each move in the same direction. This corresponds to one set of clinical observations in recovery from congestive cardiac failure (Lowe, 1953).

Although only three cases are illustrated, they are typical of many observed.

Recovery from Abnormal Osmotic Pressure

Physiological observations indicate that an increase of blood osmotic pressure increases the fluid intake and depresses the renal excretion of fluid (Gilman, 1937; Holmes and Gregersen, 1947; Verney, 1946) and *vice versa*.

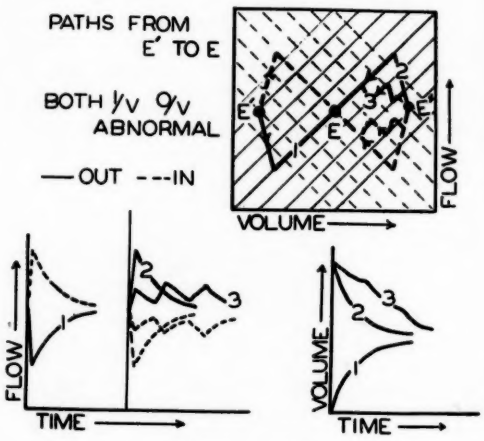


FIGURE III

Graphs showing recovery pathways of the system from abnormal equilibria (E′E″) (compare 1, 1*a*, Figure I). In these cases both the I/V and O/V relationships are abnormal, but disturbed in opposite directions

In Figure III these relationships are represented by a series of lines parallel to I and O (see Figure I) with equilibrium points at the intersection of appropriate lines. E′ represents a state of lowered osmotic pressure, and E″ a state of raised osmotic pressure.

Rapid restoration of osmotic pressure to normal would result in inflow and outflow values moving along the lines 1 and 2 (Figure III), whilst a slower and stepwise return from raised osmotic pressure would be represented by the lines 3 (Figure III). The corresponding flow and volume to time relationships are also shown in Figure III.

This particular situation could occur in association with any other flow-to-volume disturbance, so that the equilibrium point (E)

shown in Figure III need not be the normal equilibrium point of Figures I and II.

The outstanding feature of the flow-to-time relationships in these examples is that the inflow and outflow changes move in opposite directions in returning the system to equilibrium. This corresponds to another mode of behaviour seen in a proportion of patients recovering from congestive cardiac failure (Lowe, 1953). However, in these patients this type of behaviour occupies only a small portion of the total recovery time, and therefore represents a disturbance which is quickly corrected and only portion of the total abnormality.

Depression of Both Inflow and Outflow to Volume Relationship

If both the inflow-to-volume and outflow-to-volume relationships are depressed, then a new equilibrium point (E′, Figure IV) will be reached. In this case the volume at equilibrium will depend on the degree of depression of each relationship, and may be greater than, less than, or equal to normal.

In Figure IV the path from E to E′ indicates a sudden depression of both inflow and outflow mechanisms, and the path from E′ to E the sudden restoration of these to normal. The flow-to-time and volume-to-time curves are also indicated.

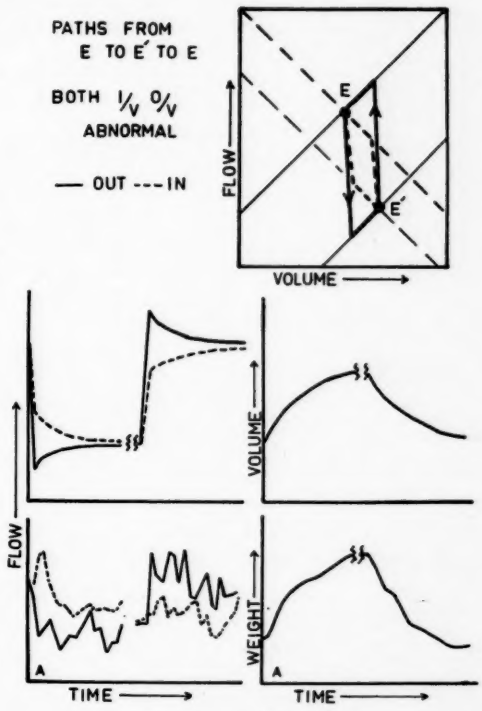
The curves A (Figure IV) were obtained from a patient suffering from hypertension who was treated with hexamethonium drugs whilst ambulatory. This led to the accumulation of œdema. After some twenty days she was confined to bed, and the phase of fluid loss ensued even though the hexamethonium drugs were administered in unreduced dosage. Although, commencing three days after confinement to bed, mercurial diuretics were administered every second day, the fluid loss phase was well established before their exhibition.

Comparison between the theoretical and the observed curves suggests that in this patient the depression and recovery of function were not sudden, but gradual or stepwise. However, the predicted and observed curves do show a similar behaviour.

RELATIONSHIP BETWEEN INFLOW, OUTFLOW AND VOLUME

In view of the good general agreement between behaviour predicted from the hypothesis and that observed in patients, it is of interest to determine qualitatively the relationship between inflow, outflow and volume.

It was assumed for the hypothesis that these relationships were linear, and the agreement observed suggests that as an approximation in the cases mentioned this may be so. However, linear relationships of this type are rare in biological situations, and it may be that the linearity is apparent only because the observations were made over limited volume and flow ranges. Further, there is



GRAPH IV

Graphs showing the pathway from a normal equilibrium (E) to an abnormal one (E′) when both I/V and O/V are depressed, and the subsequent recovery and return to E. The curves A were obtained from a patient becoming œdematous and subsequently recovering

known to be an upper limit to the amount of fluid excreted by the kidneys in a given time (Wolf, 1950), and also a lower or obligatory urine level below which flow does not fall unless the circumstances are exceptional. It might be thought, therefore, that the relationship of outflow to volume would produce a family of sigmoid curves, and that the previously quoted observations had in fact been made on the almost straight central part of such curves. It seems difficult to premise about the shape of the curve relating inflow to volume. How-

ever, the observations do suggest that the central portion of the curve is approximately straight.

Outflow

As this hypothesis indicates that the urine flow is determined by the volume of some part of the stored body fluid, then the rate of urine flow should be independent of the fluid intake, except in so far as the latter produces changes in volume of the storage. In the patients observed under standard conditions, the daily

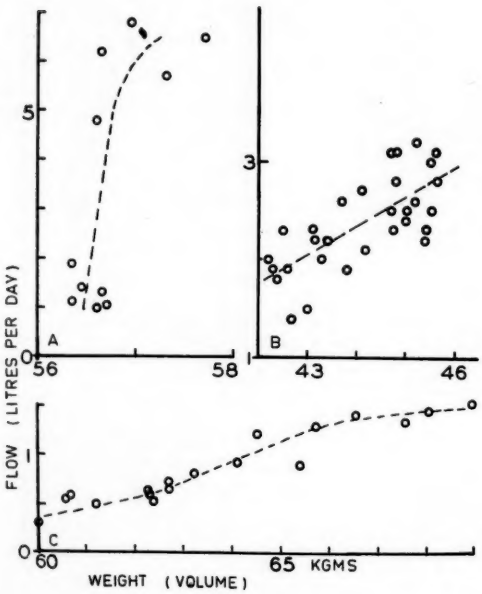


Figure V

Charts showing the relationship between urine volume per day and body weight in three patients. Patient A had normal excretory function, patients B and C had different degrees of depressed water excretory activity

output of fluid was determined under three varieties of inflow. Firstly, the daily intake was fixed at some arbitrary value, usually 1·5 to 2·0 litres; secondly, an intake as free as desired was allowed; and thirdly, the intake was deliberately changed from time to time. In all three groups the same general relationships between outflow and volume were noted. These indicate that urine flow is primarily related to volume of storage, and that the rate of fluid intake influences output only indirectly through volume changes.

In each case the value of the daily output has been plotted against body weight, and representative results are shown in Figure V. Previous observations (Fowler, 1955) have indicated that, if allowance is made for constant errors, these two measurements indicate changes in total outflow and actual fluid volume when carried out under the stated standard conditions.

The curves in Figure V are taken from abnormal conditions and can give only a general indication of trends; but they indicate a sigmoid curve for the outflow-volume relationship.

Curve A (Figure V) was obtained from a patient suffering from polydipsia following a head injury, in whom no evidence could be obtained of *diabetes insipidus*. The fluid intake was arbitrarily fixed at various levels for twenty-four-hour periods, and the urine output for each period was plotted against the body weight at the end of that period. This curve bears a striking resemblance, although at lower levels, to that reproduced by Wolf (1950) for the behaviour of a normal man under experimental water loading observed in quarter-hour intervals.

Curve V (Figure V) was obtained from a patient with Addison's disease who was somewhat dehydrated. She was treated with free fluids and a daily addition of five grammes of salt to her diet. In this instance the urine flow bears an approximately linear relationship to her increasing weight. However, the slope of the curve is much less than that of curve A and the presumed curve of normal individuals; this indicates a depression of the outflow-to-volume relationship.

Curve C (Figure V) shows the results obtained from an œdematous patient suffering from chronic nephritis, following some degree of restriction of fluid intake which produced a loss of œdema. He was in a state of gross renal insufficiency and died a few weeks after this time. It is probable that there was very little functioning renal tissue available, and the curve obtained represents a full range of function for that tissue. It is definitely sigmoid and at a very low level compared with the normal outflow-to-volume relationship.

Inflow

In the majority of the patients observed in this series the intake of fluid has not been free, but has been controlled in some arbitrary way. However, the few records of free intake available suggest that a linear relationship of intake to volume exists over short ranges of volume.

DISCUSSION

The observations recorded in this paper show that the changes in inflow, outflow and volume of body fluid predicted from the "open" system storage hypothesis can be observed in selected patients suffering from a variety of diseases. It is also apparent from the hypothesis that there are a great many abnormal situations which can occur apart from the three studied in detail. Therefore it is not to be expected that every case will clearly demonstrate these relationships when flow (in or out) is related to volume. The majority of the patients studied have had conditions which would be expected to disturb the normal relationships, and frequently more than one component of the system was abnormal. However, no instance has yet been encountered in which the changes in flow and volume could not be accounted for by the principles enunciated.

An important consequence when this hypothetical system is related to body structure is that a transport mechanism is a necessary integral part. Such a mechanism is required to carry fluid from its point of entry into the body to the various body fluid compartments and from there to the point of exit, the kidneys. The blood-stream must represent the major part of this transport mechanism; but various substances such as proteins may act as water carriers because of the power of their molecules to hold water. Disturbances of this transport mechanism must affect the relationship between inflow, outflow and volume, but all the evidence indicates a quantitative and not qualitative effect.

Disturbances of the balance of forces which control the partition of fluid within the body will upset the efficiency of the transport mechanism and produce a quantitative change in the relationships, as will variation in the amount of water diverted to temperature regulation function.

Comparison of the relationships seen in curves A, B and C of Figure V indicates that, in the abnormal states represented, not only is the outflow-to-volume relationship depressed, but the slope of the curve becomes much less steep.

It must be remembered that in the normal individual the osmotic pressure and volume are held constant only within limits, and it is necessary for this system to be in random oscillation about the equilibrium point. This means that one should speak of a normal equilibrium zone rather than a point, and this is indicated by the cross-hatched area of Figure I. As the intersecting curves obtained from the normal person are very steep, a considerable range of fluid intake and output levels exists for a small change in volume or osmotic pressure, if that is the second of the postulated controls. In the abnormal states depicted (B, C in Figure V) this equilibrium zone becomes much broader, and so the weight of such a patient becomes rather unstable.

It must be concluded that these clinical observations are in accord with the hypothesis which was advanced previously to explain various observations made on œdematous patients. The agreement between predicted events and the observations on patients indicates that the storage of fluid in the body can be satisfactorily considered as an open storage system, and subject to the laws which apply to such a system.

SUMMARY

The inflow, outflow and storage of body fluid are considered to represent an "open" storage system.

The effects of disturbance of various relationships in this system are predicted and compared with clinical observations, with good agreement.

The nature of the relationships between inflow and volume and outflow and volume are discussed.

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THE RELATIONSHIP BETWEEN BODY FLUID VOLUME AND URINE FLOW IN MAN[1]

T. E. LOWE[2]

From the Baker Medical Research Institute and Alfred Hospital Clinical Research Unit, Melbourne.

THAT the body controls its fluid volume within close limits is undisputed, and œdema states can be satisfactorily considered to be disturbances of this regulation. Further, the body fluids may in general be considered as electrolytes (solutes) dissolved in water (solvent), and both the concentrations of individual electrolytes and their total osmotic effect are controlled within similar limits.

The existence of a receptor mechanism in the brain sensitive to change in osmotic pressure of the blood has been demonstrated (Verney, 1946) and the regulation of urine flow by this centre established. However, as regulation of osmotic pressure cannot control the volume of the solvent, the existence of a volume receptor has been postulated (Welt and Orloff, 1951; Gauer *et alii*, 1951; Viar *et alii*, 1951; Luske and Palmer, 1953), although none has been conclusively demonstrated. This failure to demonstrate such a receptor mechanism and the difficulty of conceiving how it could operate have led to many doubts as to the validity of the concept of volume regulation *per se*.

In a previous paper (Lowe, 1956), we have shown that a continuous flow storage system containing "receptors" sensitive to change in volume and to change in osmotic pressure influencing both inflow and outflow of fluid could account for most of the observed behaviour of the body fluids in conditions in which volume regulation is disturbed.

It has been demonstrated both in acute experiments (Wolf, 1950) and in long-term naturally occurring conditions (Lowe, 1956) that the volume of urine flow is related to body fluid volume in a consistent manner. However, the relationship between body fluid volume and intake of fluid has not been so well defined.

In this paper some observations concerning the relationship between body fluid volume and urine flow obtained from a study of clinical states associated with disturbances of volume regulation are recorded, and some of the implications of the observations are discussed.

METHODS

The patients were all adults studied under the standardized conditions previously laid down regarding diet and observations (Lowe, 1951). Our previous experience has justified the assumption that change in body weight indicates the change in total fluid volume, and that the urinary flow indicates the outflow from the system. The patients suffered from a variety of diseases which were associated with a greater or lesser fluid loading.

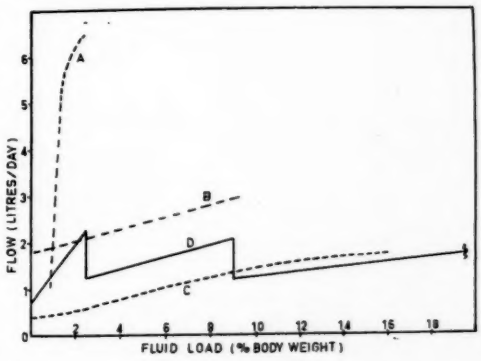

FIGURE I

Graphs showing relationship of urine flow (litres per day) to body volume (expressed as fluid load in terms of percentage of body weight); A, in a patient with polydipsia; B, in a patient with Addison's disease; C, in a patient with chronic nephritis; D, in a patient recovering from congestive cardiac failure. (See text.)

OBSERVATIONS

CASE I.—This patient, a woman, aged thirty-seven years, was suffering from polydipsia following a head injury. No evidence was obtained that this was due to *diabetes insipidus*. Curve A of Figure I relates her urine flow to body volume at various levels of fluid intake.

CASE II.—This patient was a woman, aged forty-two years, suffering from Addison's disease. Curve B

[1] Received on November 23, 1955. Part of the expenses of this investigation were defrayed by a grant from the National Health and Medical Research Council.

[2] Director of the Baker Medical Research Institute and Alfred Hospital Clinical Research Unit, Melbourne.

of Figure I was obtained when five grammes of sodium chloride were added to her diet each day. This produced a rising body weight and urine outflow.

fluid intake his weight steadily decreased, and curve C of Figure I shows the relationship between body weight and urine flow.

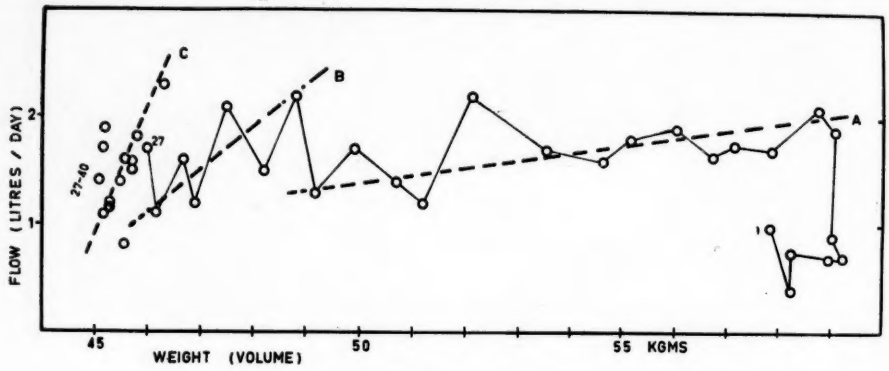

Figure II

Chart showing the daily urine flow plotted against body weight in a patient recovering from congestive cardiac failure. Numbers against the circles indicate the end of the day of observation, and the lines joining the circles indicate the path of progression. The broken lines indicate the approximate regression line of each portion of the observations

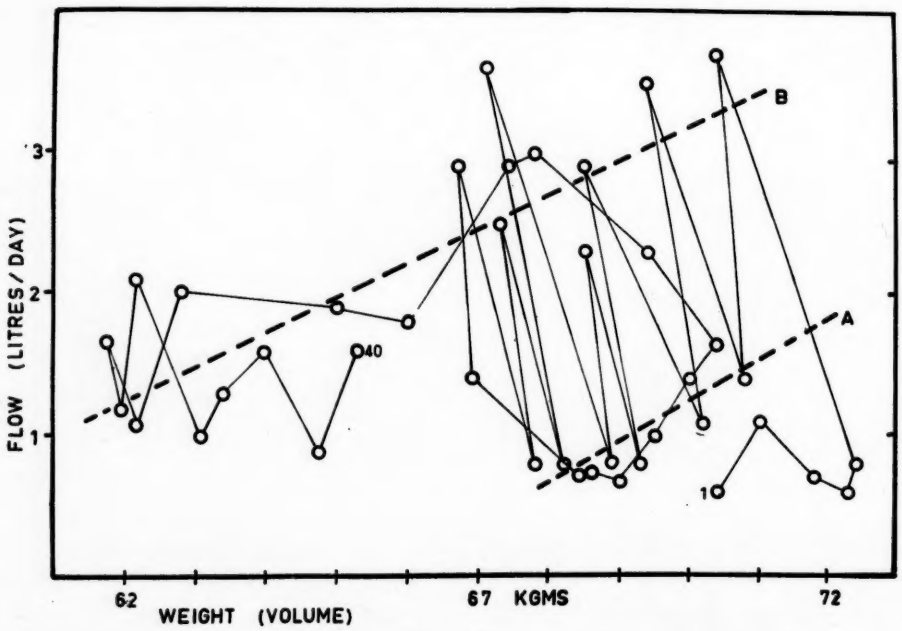

Figure III

Chart showing, as in Figure II, the progressive relationship between daily urine flow and body weight in a patient suffering from congestive cardiac failure, treated with mercurial diuretics

Case III.—This man, aged sixty-two years, was admitted to hospital in the terminal phase of chronic nephritis. He had some degree of œdema apparently following excessive fluid intake. With restriction of

Case IV.—A man, aged sixty-two years, was admitted to hospital in gross congestive cardiac failure with a fluid load of 13 litres, equal to nearly 30% of his equilibrium body weight. He was treated by

bed rest under standard conditions. Figure II shows his daily urine flow plotted against his body weight, and the lines joining the circles indicate the progression from day to day. From the seventh to the twentieth day the urine flow bears a linear relationship to the body weight (interrupted line A). At this time there is an abrupt increase in urine flow, and from the twenty-first to the twenty-sixth day a new but still linear relationship is apparent (B). Again on the twenty-seventh day there is another abrupt rise in urine flow, and for the rest of the period of observation another linear relationship is apparent (C). It will be noted that in each successive phase the slope of the line becomes steeper. This progression is also portrayed in Figure I (D).

On a second admission of this patient to hospital for gross congestive cardiac failure, these findings were almost exactly reproduced.

CASE VI.—This woman, aged forty-nine years, was admitted to hospital with a mild degree of œdema, and was found to be suffering from Addison's disease. During a period of thirteen days' observation she lost three kilograms in weight, and the line 1*a* of Figure IV shows the relation of her urine flow to body volume. On the fourteenth day oral administration of Δ-hydrocortisone (five milligrammes three times a day) was commenced. Immediately her urine flow-volume relationship moved to the line 1*b* of Figure IV, and her condition finally became stabilized near the lower end of this line.

CASE VII.—This woman was aged fifty-five years and suffered from rheumatoid arthritis. The line 2*a* of Figure IV shows the relation between volume and outflow in a preliminary observation period of six days. On the seventh day phenylbutazone, 200 milligrammes three times a day, was given, and within two days the

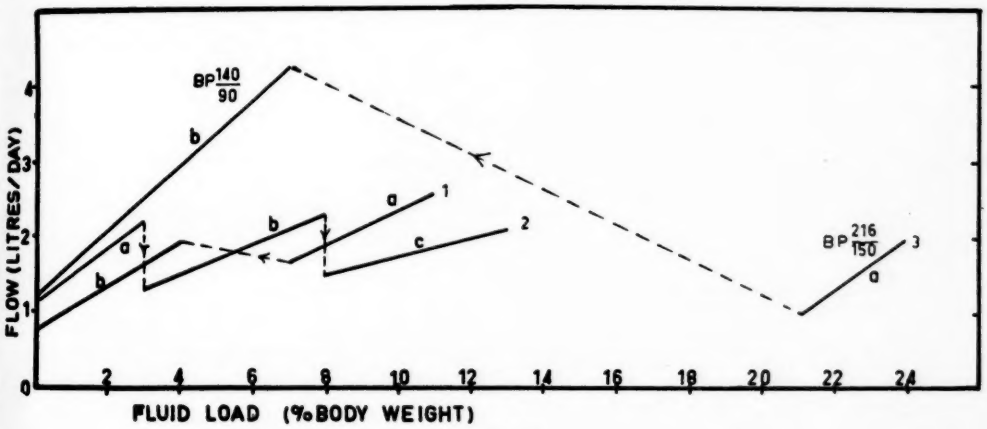

FIGURE IV

Graph showing the effect of therapeutic procedures on the relationship between daily urine flow and body fluid load in various conditions. Line 1 is from a case of Addison's disease in which cortisone moved the relationship from *a* to *b*. Line 2 is from a case of rheumatoid arthritis. Phenylbutazone produced a change from *a* to *b*, and cortisone from *b* to *c*. Line 3 is from a case of hypertension and congestive cardiac failure. A methonium drug produced the change from *a* to *b*

CASE V.—A man, aged sixty years, admitted to hospital with congestive cardiac failure, had a fluid load of eight litres. To this patient mercurial diuretics were administered every alternate day from the sixth until the nineteenth day, after which they were withheld until the twenty-sixth day; their administration was then recommenced. In Figure III the daily urine flow is plotted against body weight as in the previous case. It is apparent that in this patient two sets of linear relationships exist as indicated by the interrupted lines. One of these (B) is at a much higher level of output than the other. Inspection also indicates that in the first phase of mercurial exhibition each dose of diuretic produced a shift to the higher line, followed on the succeeding day by a return to the lower one (A). When diuretics were withdrawn on the nineteenth day the patient remained at this lower level and slowly reaccumulated fluid. Reinstitution of mercurial therapy promptly restored his outflow function to the higher level, and no longer did he fall back to the lower level on the days between injections.

outflow-volume relationship had moved to the line 2*b*. This was associated with some gain in weight. On the fourteenth day phenylbutazone was withdrawn, and 100 milligrammes of cortisone per day were administered orally. Within two days the volume-to-outflow relationship was further depressed to line 2*c*, and further weight gain ensued.

CASE VIII.—This woman, aged forty-two years, was admitted to hospital suffering from congestive cardiac failure and hypertension; her systemic blood pressure was in the region of 216 millimetres of mercury, systolic, and 150 millimetres, diastolic. During an initial observation period of twenty-eight days her volume-to-outflow relationship was represented by line 3*a* of Figure IV. On the thirtieth day pentamethonium bromide, four and a half grammes per day, was administered orally, and over a period of nine days her blood pressure fell to the region of 140 millimetres of mercury, systolic, and 90 millimetres, diastolic. From this time her volume-to-outflow relationship was represented by line 3*b*.

CASE IX.—This patient was a woman, aged forty-seven years, suffering from malignant hypertension. During a period of three days' observation her volume to outflow relationship was indicated by the lower portion of line *a* in Figure V. On the fourth day hexamethonium bromide was administered, at first intramuscularly, later orally, and over a period of five days she gained weight and the volume-to-outflow relationship moved to line *b*. The relationship continued on this line with steadily increasing weight until she was confined to bed ten days later. Immediately a weight loss began, and the volume-outflow relationship began to move towards the original line. Three days later mercurial diuretics were exhibited. By the twelfth day the volume-outflow relationship had returned to the original line and remained there. The patient gradually returned to her original weight.

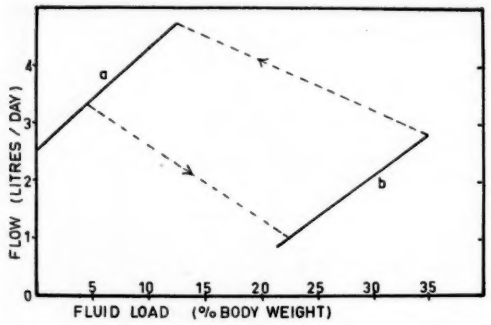

FIGURE V

Graph showing a change in outflow function from *a* to *b* induced by a methonium drug in a patient with hypertension, and the subsequent return to *a* whilst methonium was still being exhibited, but with the addition of bed rest and mercurial diuretic therapy

DISCUSSION

These observations indicate that a definite relationship exists between body volume and urine flow in a variety of disturbances of volume regulation. In most of the cases illustrated this relationship is approximately linear over the range of observations. In Cases I and III, however, the relationship produced a sigmoid curve with an approximately linear central part, and it is to be presumed that in the other cases the observations all fall into this central zone.

In Figures II and III the actual observations are plotted, and it is seen that there is a considerable scatter of points about the regression line. In fact, it might be argued that curves other than straight lines might be fitted with equal validity to these points. The fitting of straight lines to groups of observations was chosen because it has been previously demonstrated (Lowe, 1956) that frequently such a relationship can be demonstrated in less complex circumstances. Further, the change from one line to another in most instances is associated with the exhibition of some agent, such as cortisone, phenyl butazone or mercurial diuretic, which might be expected to produce a change in the output of fluid. The considerable scatter of points about the regression lines is to be expected, for it has previously been shown (Lowe, 1956) that the flow is under the control of at least two factors, of which body volume is one. Unless the second factor is moderately constant during the period of observation, then any relationship between flow and body volume may be obscured. For this reason not every case can be expected to show clearly the relationship between flow and body volume.

If only the linear parts of the curves illustrated are considered, it will be noted that there is pronounced variation in the slope, from the very steep line of the probably normal patient in Case I (Figure I, A) to the very flat curve of the chronic nephritic patient (Figure I, C). Further it will be noted that a change in relationship leading to depression of outflow (Figure IV, 2) leads also to a diminution of curve slope, and conversely improvement of function (Figure I, D) to a steepening of the line.

Another feature of these relationships is the stepwise nature of the change from one level of function to another. Frequently this is rapid (Cases IV, V, VI), but sometimes it takes many days to complete. It is also to be noted that the same agent may have opposite effects under different circumstances. Thus cortisone produces a depression of function in Case VI (Figure IV, 2) and an improvement in Case II (Figure IV, 1). Methonium compounds in Case IX produced a marked depression (Figure V), but in Case VIII produced a marked improvement in function (Figure IV, 3).

When an attempt is made to interpret the meaning of these changes, it must be remembered that it is outflow function and not renal function which is being studied. The outflow mechanism consists of both the excretory organ—the kidney—and a transport mechanism which links the excretory organ with all parts of the body fluid compartments. In such a complex system there are many points at which function could become abnormal—such, for example, as the heart, partition mechanisms, glomerular filtration and tubular reabsorption, to mention but a few in general terms. The fact that in many cases the transition from one level of function to another is abrupt suggests that the activity of one link

is abruptly changed. Thus mercurial diuretics which inhibit an enzyme system appear to produce consistent and abrupt changes. In those cases in which drug action is variable, it is possible that there is more than one site of action; thus cortisone enhances outflow function in Addison's disease, but depresses it in other conditions.

The stepwise changes seen in Case IV during the recovery from congestive cardiac failure treated by bed rest indicate that there were probably two abnormalities in the system which returned to normal at different times.

Further, in comparison with the probably normal function in Case I, none of the patients has a normal outflow-volume relationship and, as they all suffered from conditions leading to some disturbance of fluid volume regulation, they probably all had some degree of depression of outflow function even when in equilibrium at apparently normal volumes. They all showed a much wider range of normal weight than control subjects.

These observations, which show clearly a relationship between volume and urine flow, greatly strengthen the contention that there must exist within the body some receptor mechanism sensitive to change in volume of some part of the body fluids. The consistency of the results suggests that the relationship could be used as the basis of a test of outflow function, and in fact it is the depression of this relationship which is the basis of the Kepler-Power test of water excretion used diagnostically in Addison's disease. It is probable also that the relationship will be a valuable test in studying the action of various therapeutic agents.

SUMMARY

Observations on patients suffering from a variety of diseases leading to disturbances of body fluid volume regulation indicate a definite relationship between body fluid volume and urine flow.

Disease states produce quantitative changes in this relationship, and stepwise changes in the relation are often seen during both the development of and recovery from these conditions.

It is considered that these observations support the concept of a volume "receptor" within the body.

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VIBROCARDIOGRAPHY—A STUDY OF VIBRATIONS IN THE NORMAL HEART[1]

MARGARET DOWN[2]

From the Baker Medical Research Institute and Alfred Hospital Clinical Research Unit, Melbourne

THE range of vibrations associated with the heart's activity extends from the gross movement of the apex beat, through a number of intense but inaudible vibrations, into the sonic range, and up to a maximum frequency of 800 to 1000 cycles per second. At 30 cycles per second the ear is relatively insensitive, while at 1000 cycles per second it is most sensitive.

Graphic representations of heart sounds have been made for fifty years or more, but their clinical use results largely from the development of a logarithmic phonocardiograph by Rappaport and Sprague (1941). This instrument amplifies and records the sounds "stethoscopically"; that is to say, the low-frequency vibrations are selectively attenuated as they are by the human ear in auscultation. The amplitude of the deflections in a logarithmic phonocardiogram is therefore directly related to the loudness of the sounds.

The vibrocardiograph[3] differs from the phonocardiograph, in that it records all vibrations associated with the heart's activity according to their respective physical energy content, and this does not parallel auditory loudness. A study of cardiac vibrations in terms of intensity and frequency, the arbitrary modifications of ear and stethoscope being ignored, should give information of a character different from that gained by standard phonocardiography or clinical auscultation.

The instrument allows detailed study of vibrations in terms of energy content, intensity and duration. A rapid recording method allows easy analysis of frequencies of wave forms. A machine with similar physical characteristics — the "spectral phonocardiograph"—has been employed by McCusick *et alii* (1954). In this instrument, although the frequency spectrum is separated by filter systems similar to those of our vibrocardiograph, accurate analysis of individual frequencies is hindered by the recording method adopted, since vibrations appear as dark smudges—not sinusoidal wave forms—in the appropriate filter band. Intensity is estimated by the darkness of the silhouette, and interpretation may be more difficult. It is considered that the vibrocardiograph may have advantages over the "spectral phonocardiograph" in frequency and intensity analyses.

The present study has been undertaken with a view to extending knowledge regarding the vibrating structures of the heart. The immediate aim is to define the characteristics of cardiac vibrations in normal individuals.

APPARATUS AND METHOD

The vibrocardiograph (Figure I and appendix) used in this study may be described briefly as follows. The currents generated in a crystal microphone, placed at the appropriate site on the chest wall, are passed through a series of five selective filters which separate the vibrations into narrow frequency bands. These bands are then amplified and displayed simultaneously on cathode-ray oscilloscopes, and photographed with a high-speed camera. The following five channels are available:

Channel I	..	0 to	50	cycles per second
Channel II	..	30 to	130	cycles per second
Channel III	..	130 to	260	cycles per second
Channel IV	..	260 to	480	cycles per second
Channel V	..	480 to	1000	cycles per second

Owing to technical difficulties in obtaining an adequate time constant in Channel I, recordings from this frequency band were unavailable, except in a few of the later cases,

[1] Received on November 22, 1955. The expense of this investigation was defrayed by a grant from the Life Insurance Medical Research Fund of Australia and New Zealand.

[2] Research assistant, Baker Medical Research Institute and Alfred Hospital Clinical Research Unit, Melbourne.

[3] The term "vibrocardiograph" has been recommended at International Cardiological Congress meetings in 1950 and 1953 to describe instruments which record cardiac vibrations including those below the audible range.

for the present analysis. Since no quantitative calibrator was incorporated, accurate comparisons of amplifications could not be made; but comparative amplifications were kept approximately constant. (It has been found during construction that the energy output of low-frequency vibrations associated with cardiac activity was so great that the gain—amplification—in the lower-frequency bands had to be reduced many hundreds of times compared to gain in higher-frequency channels. That is, for a given gain the amplitude of response in the low-frequency band is many hundreds of times that in the high-frequency channels.) The electrocardiogram is recorded at the same time, and a timing device is incorporated. The speed at which film is fed through the camera may be varied; but in this study a paper speed of 400 millimetres per second was used in all cases. Occasionally a paper speed of 56 millimetres per second was employed in supplementary recordings.

Tracings of cardiac vibrations were made with the microphone placed in turn at the mitral, tricuspid, aortic and pulmonary areas. External noise was effectively excluded in most cases by strapping the microphone to the chest and then covering it with a large piece of thick cotton wool. Surmounting the cotton, and directly over the microphone, a sandbag was placed. The optimal position of the microphone was judged by the deflections on a monitor screen. The tracings were made during quiet respiration.

OBSERVATIONS

A series of tracings from 53 normal individuals has been made. Of these, 25 were males and 28 were females. Their ages ranged from seventeen to fifty years, only five subjects being aged over thirty years. The criteria for normality were as follows: no past history of heart disease, normal cardiac function, no signs of abnormal auscultatory findings (any patient with a functional systolic bruit was excluded from the series), heart size normal clinically, blood pressure within normal limits.

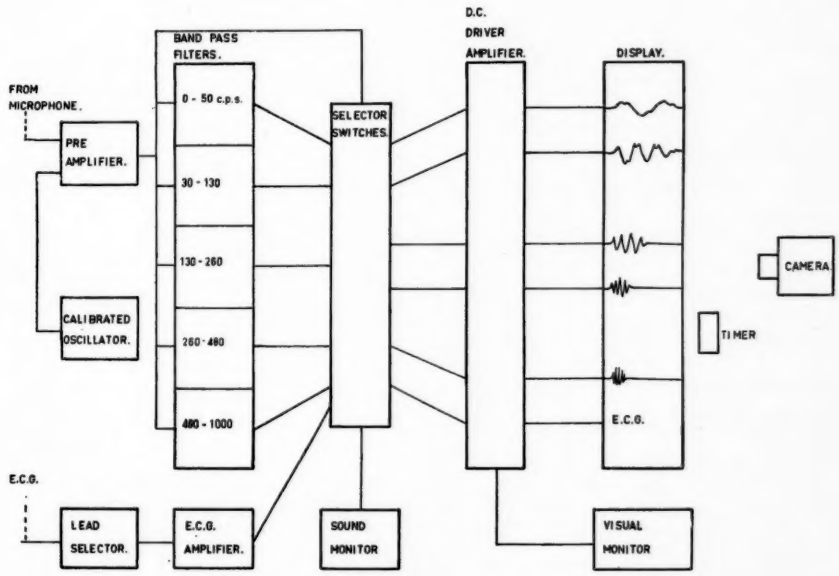

FIGURE I

Diagrammatic representation of the vibrocardiograph

The vibrations in health may be recorded as less intense in the individual who is obese or has a well-developed musculature. Presumably the increased thickness of the chest covering damps down the transmitted vibrations. Thin individuals also present technical problems in recording cardiac vibrations. Here the vibrations may be very intense and may be recorded as such; but because microphone placement is often uneven owing to deep grooving between the ribs,

external noise is frequently introduced and distorts the tracing.

The normal vibrocardiogram displayed consistent findings with regard to general form (Figures II and III). There were two dominant groups of vibrations—the first group, A, incident to the onset of systole, and the second group, B, incident to the second heart sound.

In the first vibration complex, group A, the following three groups of waves were recognisable: (i) A group of preliminary waves, one or two in number, were occasionally seen in the low-frequency channel between the *P* and *S* deflections of the electrocardiogram. These were of lower amplitude than, and immediately preceded, the principal group of waves. (ii) The principal vibration complex,

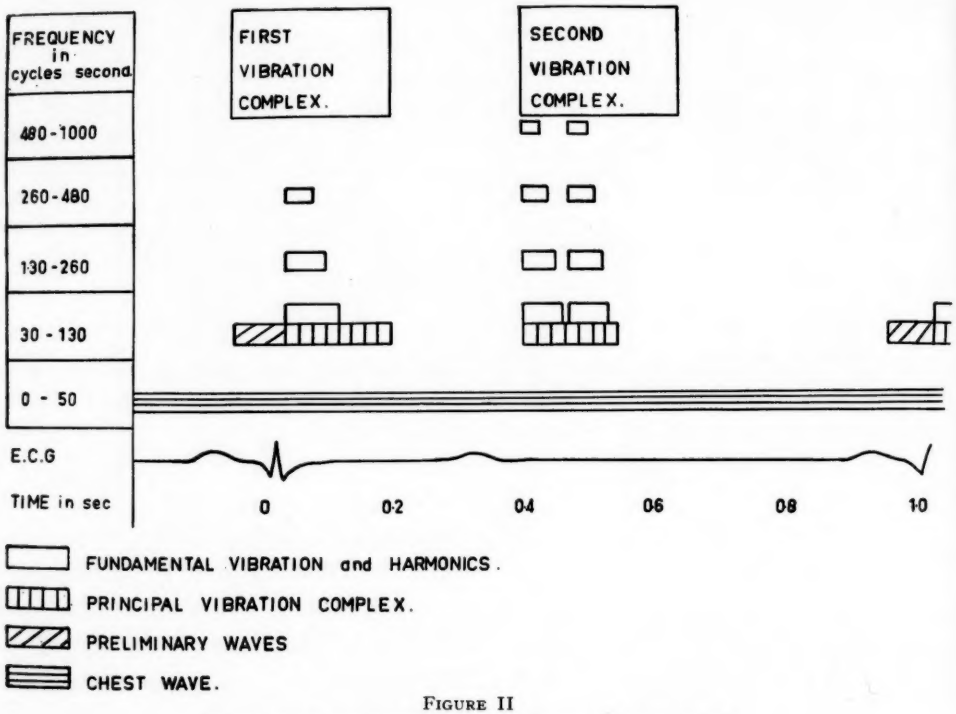

FIGURE II

Diagrammatic representation of the normal vibrocardiogram

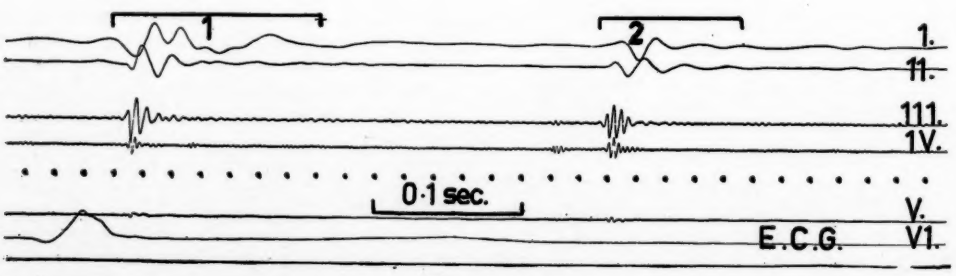

FIGURE III

Vibrocardiogram of a normal individual recorded at the mitral area. Tracing shows the first and second vibration complexes (1, 2). Note the presence of harmonic vibrations in Channels III and IV

the onset of which timed from the *Q* deflection of the electrocardiogram varied from 0·011 to 0·09 second, consisted of complex waves with frequencies ranging between 30 and 80 cycles per second. The duration of these vibrations lay in the range 0·10 to 0·26 second. (iii) Often a third element, named for convenience the fundamental vibration, could be recognized within the principal vibration complex. This element arose coincidentally with the principal vibrations, but was of shorter duration, and was often accompanied by components in the higher-frequency channels. These components were always pure tones, and their onset was always coincident with this third element or fundamental vibration, and had frequencies which were multiples of the fundamental vibration. These components were considered to be harmonics of the fundamental vibration.

The second group of vibrations coincident with the second heart sound (group B) showed characteristics similar to the first vibration complex, with the exception that there were no preliminary waves. As with the first vibration complex, harmonics were present in many cases. The onset of the second group of vibrations ranged from 0·29 to 0·46 second from the *Q* deflection of the electro cardiogram, and the duration from 0·07 to 0·143 second. This complex was of shorter duration than the complex incident to the onset of systole.

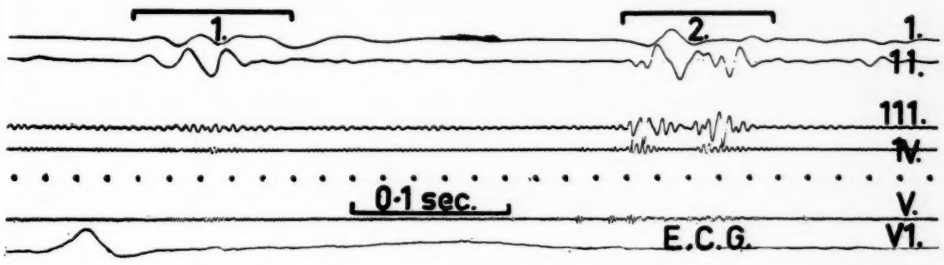

FIGURE IV

Vibrocardiogram of a normal individual recorded at the pulmonary area. Note the duplicated harmonic vibrations in Channels III and IV in the second vibration complex

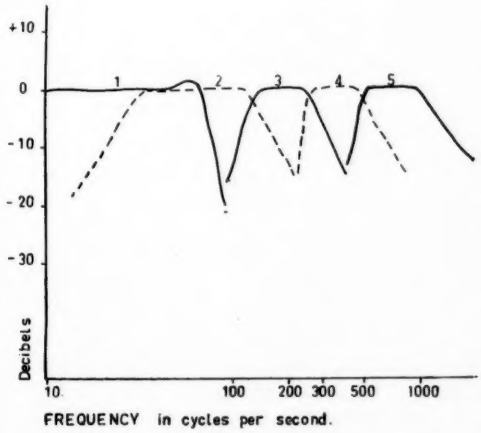

FIGURE V

Graphic display of the filter characteristics of the vibrocardiograph

The harmonics seen in association with the first and second vibration complexes are worthy of further consideration. They may be repeated in the one complex (Figure IV), and when such duplication occurs, the frequency of the two components at the one area is the same in the great majority of cases. With increasing frequency there are always decreased intensity and duration of the components, and in individual channels the intensity and duration of each component may vary. One component of a duplication present at lower frequencies may be absent from higher-frequency bands, and this is associated with less intense vibration of this component at lower frequencies. The time separation between components varies from area to area, and may be negligible. On the other hand, time separations up to 0·1 second have been recorded. In some instances the two components appear to merge. Duplication of the fundamental of both first and second main vibration complexes may occur at all areas, but is most commonly seen in the second complex at the pulmonary area (Table I).

Analysis of the relative frequency of occurrence of harmonic vibrations in first and second main complexes is set out in Table II. It will be noted that harmonics are recorded most commonly at the pulmonary area in association with the second vibration complex.

TABLE I

Frequency of Duplication of Fundamental Vibration in First and Second Main Vibration Complexes

Area	First Vibration Complex	Second Vibration Complex
Mitral	4	2
Tricuspid..	11	6
Aortic	1	8
Pulmonary	3	26

A comparison of frequencies of the harmonics in first and second vibrations complexes at each area, where there were demonstrable harmonics, did not reveal any correlation of frequencies in the two complexes (Table III).

TABLE II

Number of Cases in which Harmonic Vibrations Occurred at Various Areas

Area	Number of Cases	First Vibration Complex	Second Vibration Complex
Mitral	50	22	33
Tricuspid ..	21	15	18
Aortic	39	3	23
Pulmonary ..	50	5	48%

A comparison of frequencies of harmonics occurring in different areas in the same case again showed no correlation of frequencies.

TABLE III

Comparison of Frequencies of Vibration of First and Second Complexes

Area	Number of Cases	Harmonics with Identical Frequency in First and Second Vibration Complex	Harmonics with Different Frequencies in First and Second Vibration Complex
Mitral ..	21	12	9
Tricuspid ..	15	11	4
Aortic ..	3	2	1
Pulmonary..	6	4	2

There were 16 cases in which harmonics were of the same frequency at all areas, and 31 cases in which they differed at all or some areas.

In none of the 53 cases studied were vibrations associated with a third heart sound seen, nor was a third heart sound detected clinically.

In a few tracings in which Channel I was used, some very low-frequency, low-amplitude vibrations of five to eight cycles per second were seen to run through the entire tracing, including the period between the two main vibration complexes.

DISCUSSION

Vibrations are associated with cardiac action, and they cover a wide frequency spectrum (five to 1000 cycles per second). All these vibrations may be recorded on the vibrocardiograph used in this study, since it is not wed to a peculiar intensity-frequency response as is the human ear or the logarithmic phonocardiograph used clinically.

The normal vibrocardiogram assumes a characteristic pattern. There are two main groups of vibrations, the first incident to the onset of systole, and the second incident to the second heart sound. Occasionally, in the first main vibration complex, are seen one or two preliminary waves lying between the *P* and S deflections of the electrocardiogram. These are followed by the principal vibration complex which is an impure, intense, low-frequency vibration. Arising coincidentally with the principal vibration complex is a fundamental vibration, which is represented in higher frequency bands by harmonic vibrations. Both the fundamental vibration and its harmonics are of shorter duration than the principal vibration. The second main vibration complex does not show preliminary waves, but the principal vibration complex, fundamental vibration and harmonics may be seen. Occasionally a very low-frequency, low-amplitude wave may run throughout and between the two main vibration complexes.

Vibrations associated with cardiac activity may arise from any of the following events: (i) cardiac rotatory movements, (ii) pericardial movements, (iii) oscillation of the chest, (iv) pulsation of the large arteries within the thorax, (v) vibration of the column of blood in the heart and aorta, (vi) myocardial action *per se*, (vii) vibrations of atrio-ventricular valves with attached *chordæ tendiniæ* and papillary muscles, and vibrations of the semilunar valves.

The frequency of vibration of any of the structures mentioned above will be dependent on physical characteristics such as mass per unit length, tension, length, velocity of flow and dimensions of the associated chambers and vessels; and varying combinations of

these, depending on conditions prevailing at the time, may produce different frequencies of vibration of individual structures.

The various wave forms which together form the normal vibrocardiogram are discussed below.

1. A low-frequency, low-amplitude vibration of five to eight cycles per second was sometimes noticed. This wave runs throughout the cardiac cycle and has been described by Landes (1939–1940). It is thought to be due to oscillation of the chest as a whole—this activity being initiated by cardiac contraction. Burger and Koopman (1949) hold that this wave has definite characteristics for a particular individual.

2. Preliminary waves of low-amplitude were occasionally seen between the *P* and *S* deflections of the electrocardiogram, and preceding the first principal vibration complex. Although only a few tracings in our series exhibited these, it is reasonable to suppose that they are not artifacts, but arise in association with cardiac activity, since they always recurred at the same point in the cycle. These vibrations occur during the period of auricular systole, and may be due to vibrations of the auricular myocardium, to vibrations of the atrio-ventricular valve cusps and chordæ or to vibrations of the ventricular myocardium due to increased distension at this stage.

3. The principal vibration complex of 30 to 80 cycles per second is seen in association with both the vibrations incident to the onset of systole and the vibrations incident to the closure of the semilunar valves. These wave forms are complex and of low frequency, but may be very intense. Indeed, they are many hundreds of times more intense than high-frequency vibrations recorded. The demonstration by Smith *et alii* (1941) that cardiac muscular vibrations are of low frequency suggests that the principal vibration complex seen in the vibrocardiogram is myocardial in origin. One may reasonably regard the myocardium as a mass of individual fibres capable of vibration, and this activity may be initiated by contraction or relaxation of the myocardium in association with the first and second main complexes respectively, or may be due to vibration secondary to blood flow. Vibrations in the large arteries may contribute to the principal vibration complex. The fact that this principal vibration complex is of greater duration than the superimposed sharper waves or fundamental vibrations discussed below, supports the suggestion that the complex may be due to a structure whose physical properties lead to a prolonged vibratory response which is not readily damped—for example, myocardium and/or arterial vibrations as opposed to a valvular origin.

4. The other type of wave seen in analyses has been termed for convenience the fundamental vibration. It arises coincidentally with the principal vibration complex, but can be recognized as a separate entity of shorter duration. It is quickly damped, and in higher frequency bands may be represented by pure tones of coincident onset and frequencies which are multiples of the fundamental frequency. These higher-frequency vibrations gradually lesssn in intensity and duration as the frequency increases. It is reasonable to contend that the fundamental note emerging from the principal vibration complex has a different structural basis from the latter, and that the structure producing a fundamental vibration may resonate to produce harmonic vibrations. The brevity and clarity of these vibrations suggests an origin in a structure whose physical properties are compatible with rapid damping of vibrations. The hypothesis is entertained that the valve flaps and perhaps *chordæ tendineæ* may be the structures responsible.

In many instances the harmonics and hence the fundamental vibrations are duplicated. This may indicate that one structure is vibrating twice in rapid succession, or that two structures with similar physical properties are vibrating independently. The latter possibility seems more likely, since the time interval between the two components may vary from area to area. This variation in time interval from area to area may depend on asynchrony of the vibrating structures associated with varying respiratory or cardiac rate. The fact that the frequencies of the two components at one area are usually identical may mean that the same structure is indeed vibrating twice in rapid succession; but it may also indicate that two similar vibratory bodies are subject to similar conditions in a cardiac cycle. The fact that the harmonic frequency may vary at another area does not invalidate the hypothesis of two similar vibratory bodies, since tracings at all areas were taken in succession, not simultaneously; thus conditions prevailing in one cardiac cycle at one area are not necessarily the same as those in subsequent cycles recorded at other areas—for example, the tension or length of the vibrating structures may have altered. However, variation in harmonic frequencies at different areas may indicate that different

structures produce these vibrations at different areas.

Our recording suggests that there are four elements in both first and second heart sounds. Attention was drawn to this by Orias and Braun-Menendez (1939). In addition, some of our tracings show another element associated with the first sound—namely the preliminary wave.

It is of interest to note that the correlation between recognizable clinical splitting of heart sounds and duplication of harmonics seen in vibrocardiograms was incomplete, there being 39 cases of clinically recognizable splitting, and 61 cases of recorded duplication.

SUMMARY

An apparatus—the vibrocardiograph— which records all frequencies between 30 and 1000 cycles per second associated with the heart's activity, is described.

It is pointed out that vibrations recorded do not necessarily correspond to clinical auscultatory findings.

A study of cardiac vibrations in 53 normal subjects has been made, and the tracings were generally similar. They have been analysed with regard to onset after the *Q* deflection of the electrocardiogram, duration, intensity and frequency of vibration.

Possible structural bases for the different types of vibrations have been considered, but further studies are necessary to verify these postulates.

ACKNOWLEDGEMENTS

It is a privilege and a pleasure to acknowledge my indebtness to Dr. T. E. Lowe, Director of the Baker Medical Research Institute and Alfred Hospital Clinical Research Unit, for his valuable advice during this investigation, and for help in the preparation of this paper. My gratitude is also due to the other members of staff of the Institute for their willing cooperation. Dr. J. R. E. Fraser was associated with the development of the vibrocardiograph while having tenure of a grant from the Life Insurance Medical Research Fund of Australia and New Zealand. My thanks are also due to this Fund for the grant which has defrayed the expenses of this investigation.

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APPENDIX

The vibrocardiograph consists of a crystal microphone fed into a four-stage resistance coupled pre-amplifier having a maximum amplification of 10,000. From the pre-amplifier the signal is fed into the inputs of five resistance-coupled feedback filters of the band-pass type.

The outputs of the pre-amplifier and all five filters are then fed into a selector switch, so that a variety of phenomena may be displayed simultaneously on the six cathode ray displays.

The output of an electrocardiograph amplifier is also fed into the selector switch, so that an electrocardiogram may be recorded as a physiological marker. A lead selector switch is incorporated on this amplifier, together with provisions for recording phlebograms.

Both sound and visual monitors are connected into the display selector switch unit, so that the whole or any filtered portion of the signal may be monitored.

From the selector switch unit the six desired signals are fed into the cathode ray tube driver direct current amplifiers, into which are incorporated the Y-axis positioning controls. The outputs of the direct current amplifiers are connected directly to the X-axis plates of three double-beam cathode ray tubes.

The cathode ray tubes are double-gun types, giving two separate and independent beams which have their own intensity, focus and positioning controls. An electronic X-axis sweep can be switched in to give visual monitoring on all channels. In addition, a separate double-gun tube with its associate circuits and amplifiers can be switched to any channel and used as a visual monitor during the photographing.

A synchronous-motor light chopping device was placed near the cathode ray tubes, and its light source directed into the camera lens gives a dot every fiftieth of a second.

The camera used is a Southern Instruments Universal camera M731 of variable speed, and uses photographic recording paper 70 millimetres wide.

The whole unit was mounted in two standard dimension six-foot racks, the camera being mounted separately 15 inches away.

Characteristics

Microphone.—The unit used was a "Zephyr" 1×A crystal insert placed in a sealed "Perspex" case, the cavity being four centimetres in diameter. The frequency response was within ±0·5 decibel from 30,000 to 100 cycles per second, —3·0 decibel at 100 cycles per second, —8·0 decibels at 50 cycles per second, and about —14 decibels at 30 cycles per second. Distortion of any consequence was not suspected at any frequency recorded. Any resonance was well outside operating frequencies.

Filters.—Filter characteristics of the vibrocardiograph are represented in Figure V. It is noted that in Channel I recordings are 180° out of phase, and frequencies of 15 cycles per second have time delay of approximately three milliseconds.

Calibration.—No attempt was made to calibrate the microphone in terms of the sound energy entering it. However, a comparative calibration was made by feeding into the microphone input circuit a signal of known frequency and voltage from an "Ediswan" variable frequency oscillator with a calibrated attenuator.

CHANGES IN THE ELECTROCARDIOGRAM DURING PREOPERATIVE HYPOTHERMIA IN MAN[1]

DONALD EMSLIE-SMITH[2]

From the Baker Medical Research Institute and Alfred Hospital Clinical Research Unit, Melbourne

MANY reports of experimental hypothermia in dogs have included references to changes in the electrocardiogram, but only a few observers have reported alterations in the human electrocardiogram at low body temperatures, either from victims of accidental exposure to cold (Tomaszewski, 1938; Graybiel and Dawe, 1948; Laufman, 1951) or from patients deliberately cooled (Kossmann, 1940). It has therefore been thought desirable to describe the consistent and conspicuous changes which have been observed during the preoperative production of hypothermia in five patients.

SUBJECTS AND METHODS

Each of the five patients had suffered a recent subarachnoid hæmorrhage from a congenital cerebral aneurysm. There were four women and one man, and their ages ranged from twenty-seven to forty-seven years. Hypothermia was produced in preparation for craniotomy. One patient (Case II) had hypertensive heart disease; two patients Cases III and V) had moderate diastolic hypertension at the time of observation, but no clinical or electrocardiographic evidence of heart disease; the other two had no cardiovascular abnormality.

Anæsthesia was induced by the intravenous administration of thiopentone or pentobarbitone, or with nitrous oxide and ether, and was maintained with nitrous oxide and oxygen, after laryngeal intubation with the use of succinyl choline followed by tubocurarine. Respiration was controlled when necessary. Hypothermia was produced by the application to the skin of ice in plastic bags. Autonomic responses to cold were depressed by the intravenous administration of hypotensive and autonomic blocking drugs in various combinations — trimethaphan camphonate ("Arfonad") together with pethidine and hydrogenated ergot alkaloids ("Hydergine"), with or without promezathine.

After the patients had been anæsthetized, but before they were cooled, the electrocardiogram was recorded, standard and unipolar limb leads with two or more præcordial V leads being used. While the body temperature was falling, moment to moment changes in the electrocardiogram were observed on a cathode ray oscilloscope ("Electrocardioscope", Cambridge Instrument Company Limited),

[1] Received on December 19, 1955.

[2] Edward Wilson Memorial Research Fellow.

TABLE I

Measurements from Electrocardiograms of Five Anæsthetized Patients Before and After Cooling

Case Number	Rectal Temperature (°C.)	Heart Rate (Beats per Minute)	*RR* (Seconds)	*PR* (Seconds)	*QS*[1] (Seconds)	*QT* (Seconds)	*QTc* (Seconds)
I	"Normal"	87	0·69	0·12	0·05	0·37	0·45
	29·0	37	1·64	0·23	0·05	0·70	0·55
II	36·5	87	0·69	0·16	0·07	0·44	0·53
	29·0	45	1·32	0·20	0·07	0·67	0·58
III	36·5	71	0·84	0·12	0·03	0·44	0·48
	27·2	28	2·16	0·18	0·03	0·74	0·50
IV	36·6	105	0·57	0·14	0·05	0·36	0·48
	29·0	60	1·00	0·17	0·05	0·54	0·54
V	36·8	104	0·58	0·14	0·04	0·37	0·49
	28·5	40	1·50	0·21	0·04	0·74	0·60

[1] Measured from the onset of *Q* to the end of the intrinsicoid deflection.

and permanent records were made by the use of a hot wire, direct writing electrocardiograph ("Electrite", Cambridge Instrument Company Limited). Rectal temperatures were measured by a thermistor recorder (Bayliss Electronics).

From the permanent electrocardiograms the following intervals were measured and calculated: *RR*, *PR*, *QT*, *QTc* $\left(\frac{QT}{\sqrt{RR}}\right)$ and "*QS*"—measured from the onset of *Q* to the end of the intrinsicoid deflection. This arbitrary interval was chosen because in some leads the conventional *QRS* interval was lengthened by a slow deflection which, it was considered, more properly belonged to the *ST* segment.

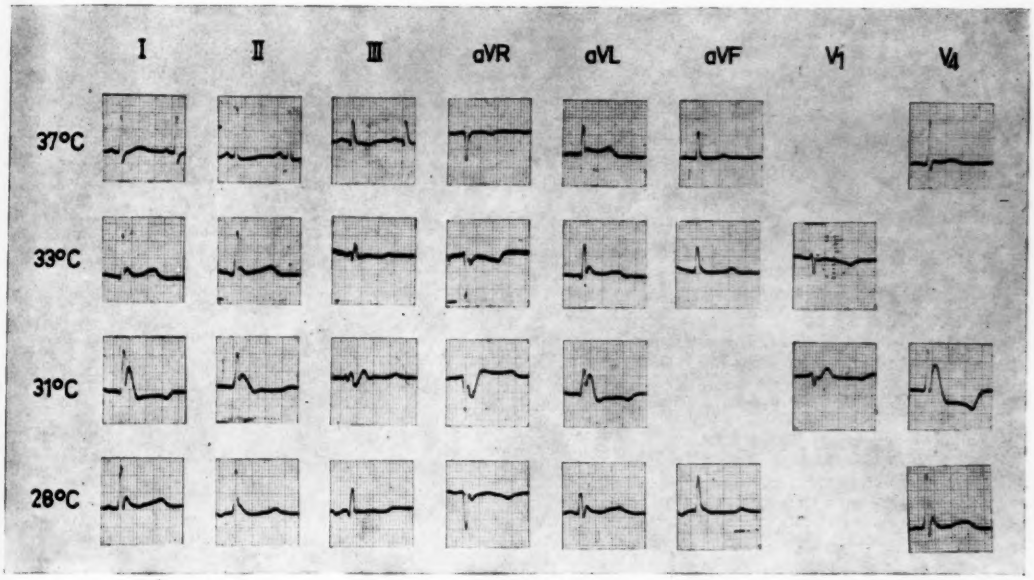

FIGURE I

Case I: Changes in the electrocardiogram during cooling, showing the conspicuous slow upward deflection early in *ST*, and the *T* inversion in leads I, aVL and V_4, at 31° C. (Although the rectal temperature at the time of the last row of tracings was 28° C., the temperature of the blood returning to the heart was probably higher than at the time of the previous tracings)

OBSERVATIONS

General

In all cases as the temperature fell the heart rate slowed, and the *PR*, *QT* and *QTc* intervals increased. The interval "*QS*" remained constant (Table I).

Consistent changes developed in the early part of the *ST* segment in some leads from all patients. In general these changes consisted either of a widening of the base of the *QRS* complex, with or without the appearance of a ledge on the descending limb of *R* or the ascending limb of *S*, or else of a conspicuous, discrete, slow deflection early in *ST*, but apparently separate from the *QRS* complex. This deflection was upward in leads related to the left ventricle (aVL or aVF and left præcordial leads) and downward in lead aVR. In tracings from one patient (Case I), this slow upward deflection was present in rudimentary form before cooling began.

Detailed Description of the Changes in the Electrocardiogram

CASE I.—The electrocardiographic tracings before and during cooling are shown in Figure I.

Before cooling, normal sinus rhythm is present. This is a normal electrocardiogram with intermediate heart position. Leads aVL and V_4 resemble one another: the *ST* segment is elevated slightly above the isoelectric line; immediately after the *QRS* complex in the early *ST* segment there is a slow upward deflection of an amplitude slightly less than *T*. The *T* wave is upward in leads I, aVL, aVF and V_4, downward in leads II, III, aVR.

During cooling, there is lengthening of *RR*, *PR*, *QT* and *QTc*. There is the appearance or an increase in amplitude of slow deflections early in the *ST* segment, upward in leads I, II and aVL, downward in leads

aVR and V_1, with widening of the base of the *QRS* complex in aVF. As the temperature falls these deflections increase in amplitude, until at 31° C. they are very conspicuous and the *T* wave has become inverted in some leads—that is, downward in leads I, II, aVL, V_1 and V_4, upward in leads III and aVR. On warming the patient, these changes regress; but after the rapid intravenous infusion of ice-cold blood they quickly become again more obvious, with inversion of the *T* wave (Figure II).

CASE II.—Before cooling, there is normal sinus rhythm. The heart is in the horizontal position with evidence of "left heart strain" (the *T* wave is downward in leads I and aVL, and flat in leads V_5 and V_6).

During cooling, there is lengthening of *RR*, *PR*, *QT* and *QTc*. There is the appearance and increase in size of a slow deflection early in the *ST* segment in leads II, III and aVF and in the left precordial leads. This deflection is not so conspicuous as in Case I.

CASE III.—Before cooling, there is normal sinus rhythm. The heart position is horizontal. The *rS* pattern in lead V_4 without *qR* in lead aVR suggests some clockwise rotation. The *T* wave is upward in leads aVL and V_4.

During cooling, there is lengthening of *RR*, *PR*, *QT* and *QTc*. The slow deflection early in the *ST* segment appears in lead V_4, but is seen only as a ledge on the downstroke of *R* in lead aVL and on the upstroke of *S* in lead aVR. At lower temperatures the *T* wave becomes diphasic (downward and then upward) in lead V_4 and, later, in lead aVL.

CASE IV.—The electrocardiographic tracings before and during cooling are shown in Figure III.

Before cooling, there is normal sinus rhythm. The heart position is vertical. There is minimal depression of *ST* take-off in leads II, III and aVF, and flattening of the *T* wave in lead aVF. The *P* wave is large in leads II, III and aVF.

During cooling, there is lengthening of *RR*, *PR*, *QT* and *QTc*, with widening of the base of *QRS* in leads I and V_1. There are the appearance and increase in size of slow deflections early in the *ST* segment, upward in leads II, III, aVF and V_4, and downward in leads aVR and aVL. No change in the direction of the *T* wave occurs.

CASE V.—The electrocardiographic tracings before and during cooling are shown in Figure IV.

Before cooling, there is normal sinus rhythm. The heart position is horizontal. The *T* wave is upward in lead V_1, slightly flattened in lead aVL.

During cooling, there is lengthening of *RR*, *PR*, *QT* and *QTc*, with widening and "ledging" of the base of the *QRS* complex in lead I. There are the appearance and increase in size of deflections early in the *ST* segment, upward in leads II, V_4R^3, V_1, V_4 and V_5, downward in leads aVR and V_7. The *T* wave is inverted in lead V_1 at 30·5° C.

DISCUSSION

A consistent pattern of changes in the *ST* segment and the *T* wave is seen on cooling patients to 31°C or lower. The most conspicuous feature of this is the appearance and increase in amplitude of an upward deflection in the early part of the *ST* segment in leads probably related to the left ventricle. This deflection is inscribed too slowly to resemble an ordinary "secondary" *R* (*R'*). Its appearance in precordial leads to the left and right of the chest does not resemble the pattern of either right or left bundle-branch block (Figure V).

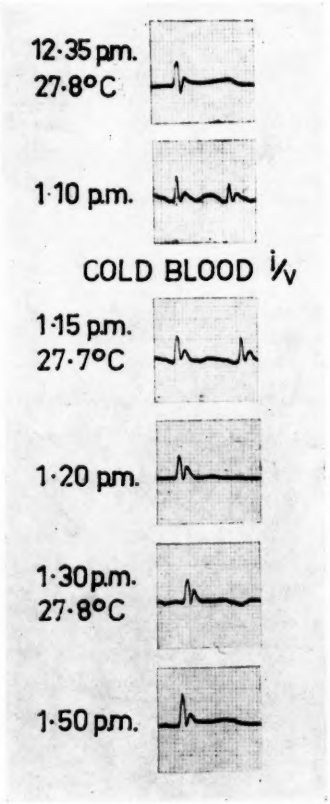

FIGURE II

Case I: The effect of a rapid intravenous infusion of very cold blood. The rectal temperature remains constant, but the slow upward deflection early in the *ST* segment becomes higher in relation to *R* (amplification not constant), and the *T* wave becomes flattened and then inverted. The changes are temporary

and is not like any commonly encountered pattern of injury. It is sometimes present in rudimentary form in the electrocardiogram at normal temperatures (Figure I). When this deflection reaches a high amplitude, the *T* wave

may become flat and later inverted. These changes occur in different degree and at different temperatures in individual patients.

Kossmann (1940) observed a similar deflection in four patients who underwent deliberate therapeutic hypothermia. He suggested that it might be evidence of the dipolar nature of the regression process in cardiac muscle postulated by Macleod (1938). Laufman (1951) noticed the same deflection in his patient with accidental hypothermia, but attempted no explanation. Tracings recorded by Tomaszewski (1938) from an accidentally frozen patient showed in the standard limb leads the fully developed pattern of slow upward deflection and inverted *T* wave. These changes were thought to be the result of a defect in intraventricular conductivity.

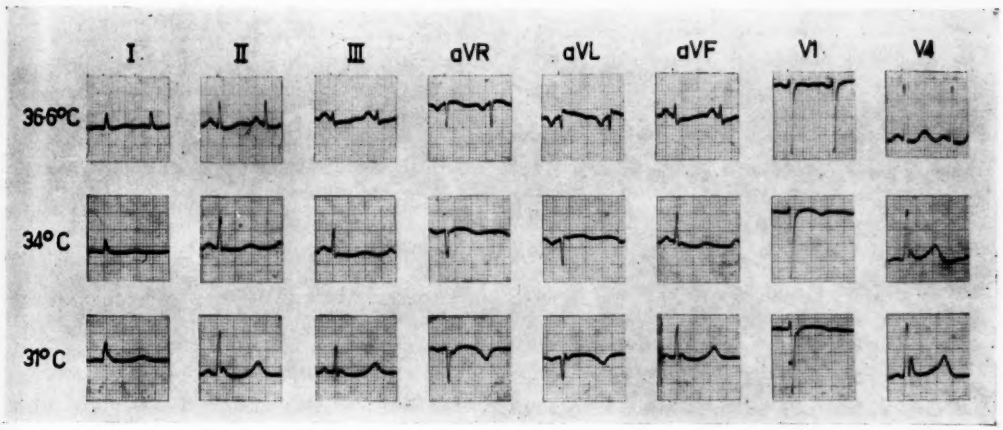

FIGURE III

Case IV : Changes in the electrocardiogram during cooling, showing, at 31° C. (rectal), conspicuous slow deflections early in the *ST* segment (upward in leads II, III, aVF and V_4, downward in leads aVR and aVL), and the widening, with " ledging ", of the base of the *QRS* complex in leads I and V_1

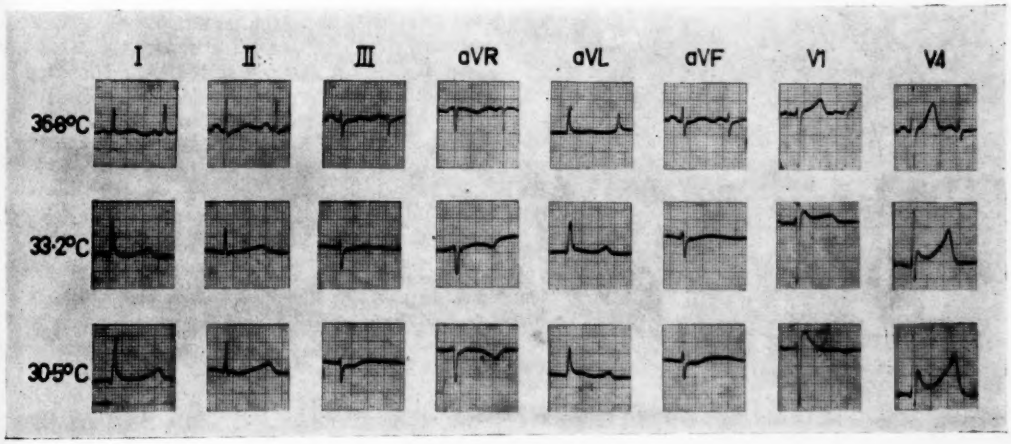

FIGURE IV

Case V : Changes in the electrocardiogram during cooling, showing, at 30·5° C. (rectal), conspicuous, slow, upward deflections early in the *ST* segment in leads II, V_1 and V_4, and widening, with " ledging ", of the base of the *QRS* complex in leads I, aVR and aVL. The *T* wave in lead V_1 is now inverted

A similar deflection has been seen by several workers, and in this laboratory (Figure VI), during the production of experimental hypothermia in dogs. It has been variously attributed to myocardial anoxia (Juvenelle, 1952; Blades and Pierpont, 1954), to an

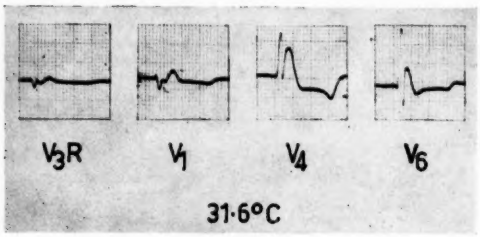

FIGURE V

Case I: Precordial leads showing a pattern unlike that seen in either right or left bundle-branch block

injury current (Osborn, 1953), to acidosis (Osborn, 1953; Covino and Hegnauer, 1955), or even to auricular repolarization (*Ta* segment) (Siems *et alii*, 1955). Covino and Williams (1955) have demonstrated in dogs that during the time occupied by the deflection,

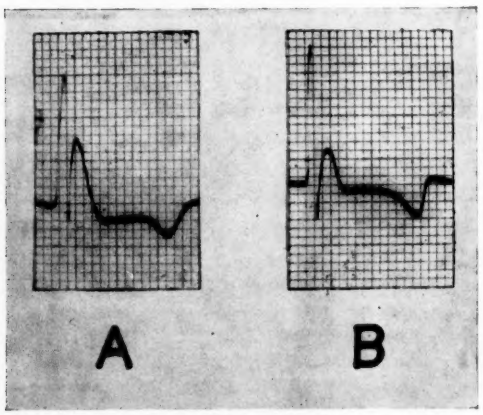

FIGURE VI

A, Case I; precordial lead V_4 at 32° C. (rectal). B, direct electrogram from epicardium of left ventricle of dog at 25·2° C. (œsophageal)

the threshold of cardiac muscle to artificial stimulation is strikingly reduced. Covino and Hegnauer (1955) have now reported the production of both the deflection and the hyperexcitable state in normothermic dogs made acidotic by breathing 20% carbon dioxide or by lactic acid injected intravenously. On the other hand, tracings recorded by Altschule and Sulzbach (1947) from acidotic patients do not resemble those reported here.

It seems clear, whatever the mechanism, that the process of producing hypothermia in these patients alters the total unbalanced electrical activity of the myocardium during the repolarization process, thus producing these characteristic changes in the *ST* segment and the *T* wave. The corresponding changes in the hypothermic dog are at present being studied in this laboratory and may help to simplify the problem.

SUMMARY

The electrocardiographic changes which occurred in five patients during the preoperative production of hypothermia are described.

In all cases the heart rate slowed, and *PR* and *QTc* lengthened. Consistent changes developed in the *ST* segment and the *T* wave in all cases, though differing in degree and in the temperature at which they appeared. A slow deflection early in the *ST* segment appeared, and grew in amplitude; when it became relatively high the *T* wave became inverted.

It is concluded that the process of producing hypothermia alters the repolarization process in the human heart.

ACKNOWLEDGEMENTS

I should like to thank Mr. K. C. Bradley for permission to study and report these cases, and Dr. R. H. Orton and Dr. T. E. Lowe (Director of the Baker Medical Research Institute and Alfred Hospital Clinical Research Unit) for their encouragement and help in the preparation of the manuscript.

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ADDENDUM

Since this paper was submitted for publication, a report by Börrck and Johansson has become available. (Biörck, G., and Johansson, B. (1955), " Comparative Studies on Temperature Effects upon the Electrocardiogram in Some Vertebrates ", *Acta physiol. scandinav.*, **34**, 257.) These authors give illustrations of lead II tracings from two adult patients admitted to hospital with a rectal temperature of about 30° C. Both tracings show the characteristic slow upward deflection early in the *ST* segment.

Proceedings of The Royal Australasian College of Physicians

Office-Bearers

Council has elected the following Fellows as the Office-bearers of the College to take office at the Annual Meeting on March 20, 1956, for the period 1956–1958: President, Dr. E. G. Sayers (New Zealand); Vice-Presidents, Dr. C. H. Fitts (Victoria), Dr. Bruce Hunt (Western Australia); Censor-in-Chief, Dr. T. M. Greenaway (New South Wales); Honorary Secretary, Dr. H. Maynard Rennie (New South Wales); Honorary Treasurer, Dr. W. P. MacCallum (New South Wales).

Membership

Admission of Members. The following candidates who were successful at an examination held in Melbourne in October, 1955, were admitted as Members of the College: W. M. Barnett, E. S. Bean, G. P. Brew, B. Clerehan, M. J. R. Drew, J. H. T. Ellard, J. F. Farrar, I. C. Goy, J. M. Greenaway, J. D. Harley, W. J. Hensley, W. M. Maxwell, G. Mitchell, W. G. Miller, J. F. Niall, A. H. Penington, J. R. Read, C. A. Rigg, R. E. Russell, M. Sadka, J. N. Santamaria, A. W. Steinbeck, E. Stock, J. H. E. Voss.

Honours. Dr. C. G. McDonald, of Sydney, has been created a Commander of the Order of the British Empire.

Obituary. The Council records with regret the death of Dr. F. H. Beare, of Adelaide, of Dr. R. P. McMeekin, of Melbourne, and of Dr. T. G. Short and Dr. H. W. Wilson, of New Zealand, who were Fellows of the College.

General

Visit of Dr. George F. Strong. The President of the American College of Physicians, Dr. George F. Strong, F.A.C.P., F.R.C.P. (C.), of Vancouver, Canada, will visit Australia and New Zealand during March, 1956, on a goodwill visit to the College. He will be accompanied by Mrs. Strong. Dr. Strong will be present at the Annual Meeting in Wellington from March 20 to 23, and will deliver the Arthur E. Mills Memorial Oration under the title "The Changing Aspects of Medicine".

Grants for Research. During the year 1955 grants were made from the Research Fund of the College as follow: Dr. B. P. Billington, at the Department of Medicine of the University of Sydney, for the investigation of the maximum histamine-stimulated acid production of the stomach in man; the Clinical Research Unit of the Royal Prince Alfred Hospital, Sydney, a grant-in-aid for work to be carried out by Dr. B. G. Firkin on serum proteins, proteins in lymph nodes and the proteins in the spleen, with particular regard to γ globulin immunity; Dr. V. M. Hercus, at the Clinical Research Unit of the Royal North Shore Hospital, Sydney, for cation and body fluid studies.

Scholarships. The Wunderly Travelling Scholarships in Thoracic Disease for 1956 have been awarded to Dr. John Beveridge, of New South Wales, and Dr. Bryan Gandevia, of Victoria. The Travelling Scholarship in Medicine and the Allied Sciences for 1956 has been awarded to Dr. J. G. Richards, of New South Wales.

Proposed Adolph Basser Fellowship in Research. Council has decided to establish a Research Fellowship, to be entitled the Adolph Basser Fellowship in Research of The Royal Australasian College of Physicians. It is intended that the appointment shall be made in the first instance for a period of five years, provision being made not only for the salary of the Fellow but for subventions for technical assistance and overhead expenses at the institution at which the Fellow will be working. The Fellowship will be advertised throughout the English-speaking world; but the research work must be carried out within Australia or New Zealand in a place to be selected by the Fellow.

Meetings of the College. The Annual Meeting in 1956 will be held at Wellington, New Zealand, from March 20 to 23; the Ordinary Meeting in 1956 will be held in Melbourne from October 10 to 13. The Annual Meeting in 1957 will be held at Brisbane.

Report of Committee on Occupational Health. Council has adopted the report of the Committee appointed to consider the subject of occupational health in Australia, including its place in medical practice and its teaching, investigational and legislative aspects, and to make recommendations for its development. This report will be circulated to appropriate institutions and individuals throughout the Commonwealth.

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